December 2007, Volume 246, Issue 6 , pp. 911-1119

Presidential Address

911 Why Should Young Doctors Choose to Become Surgeons?
Peter Neuhaus, MD, PhD

Original Articles

916 Long-term Results of Intersphincteric Resection for Low Rectal Cancer.
Reza Chamlou, MD; Yann Parc, MD, PhD; Tabassome Simon, MD, PhD; Malika Bennis, MD; Nidal Dehni, MD; Rolland Parc, MD; Emmanuel Tiret, MD
In the treatment of very low rectal cancer, a distal resection margin of more than 1 cm can be obtained by partial internal sphincteric resection, allowing sphincter preserving surgery with good oncologic results. Such technique achieves good functional results in 75% of patients.

923 Pancreatic Head Resection With Segmental Duodenectomy: Safety and Long-Term Results.
Akimasa Nakao, MD, PhD; Laureano Fernández-Cruz, MD, PhD, FRCS
This prospective study from Nagoya (Japan) and Barcelona (Spain) evaluates the usefulness and long-term results with pancreatic head resection with segmental duodenectomy (PHRSD; Nakao's technique) in patients with branch-duct type IMPT. The major advantages of PHRSD are promising long-term results in terms of pancreatic function (exocrine and endocrine) with important consequences in elderly patients. PHRSD should be considered as an organ-preserving pancreatic resection for the branch-duct type of intraductal papillary mucinous neoplasm located at the head of the pancreas.

932 18-Fluorodeoxyglucose Positron Emission Tomography Enhances Computed Tomography Diagnosis of Malignant Intraductal Papillary Mucinous Neoplasms of the Pancreas.
Cosimo Sperti, MD; Sergio Bissoli, MD; Claudio Pasquali, MD; Laura Frison, MD; Guido Liessi, MD; Franca Chierichetti, MD; Sergio Pedrazzoli, MD, FACS
Sixty-four patients with a suspected pancreatic intraductal papillary mucinous neoplasm (IPMN) underwent computed tomography (CT), magnetic resonance (MR) + magnetic resonance cholangiopancreatography (MRCP) and 18-fluorodeoxyglucose positron emission tomography (18-FDG PET). PET was better than CT and MR in diagnosing malignancy with a higher sensitivity (92% vs. 58%) and specificity (97% vs. 82%).
Use of Severely Steatotic Grafts in Liver Transplantation: A Matched Case-Control Study.
Lucas McCormack, MD; Henrik Petrowsky, MD; Wolfram Jochum, MD; Beat Mullhaupt, MD; Markus Weber, MD; Pierre-Alain Clavien, MD, PhD, FACS, FRCS (Eng), FRCS (Ed)
This study challenges the policy of most transplant surgeons not to use severely steatotic liver grafts for cadaveric liver transplantation. The cohort demonstrates that cadaveric liver transplantation of severely steatotic liver grafts can achieve similar results compared with patients without severe steatosis when appropriately allocated.

Jan P. Lerut, MD, PhD; Giuseppe Orlando, MD; Rene Adam, MD, PhD; Marcello Schiavo, MD; Jurgen Klempnauer, MD; Darius Mirza, MD; Emmanuel Boleslawski, MD; Andrew Burroughs, MD, PhD; Carlos Fernandez Sellés, MD; Daniel Jaeck, MD; Robert Pfitzmann, MD; Mauro Salizzoni, MD; Gunner Söderdahl, MD; Rudi Steininger, MD; Andre Wettergren, MD; Vincenzo Mazzaferrro, MD; Yves Patrice Le Treut, MD; Vincent Karam, PhD; European Liver Transplant Registry
This is the first large study with long-term follow-up to focus on the value of liver transplantation in the treatment of hepatic epitheloid hemangioendothelioma, a rare vascular hepatic disorder. The results suggest a more aggressive attitude toward hepatic epitheloid hemangioendothelioma seems to be warranted after a thorough staging of the disease. This attitude remains valid even in the presence of close (lymph nodes) or distant extrahepatic disease localization.

Localized Hepatic Ischemia After Liver Resection: A Prospective Evaluation.
Philippe Gertsch, MD; Riccardo E. Vandoni, MD; Angelo Pelloni, MD; Aljosa Krpo, MD; Mario Alerci, MD
Enhanced computed tomodensitometry was systematically performed on 150 patients receiving hepatectomies within 48 hours after surgery. Localized ischemia was detected in 25% of patients. The occurrence of ischemia was independent of the type and the extent of hepatectomy. A higher incidence of biliary leakage was observed in these patients.

Is There Still a Role for Total Pancreatectomy?
Michael W. Müller, MD; Helmut Friess, MD; Jörg Kleeff, MD; Rolf Dahmen, MD; Markus Wagner, MD; Ulf Hinz, MSc; Daniela Breisch-Girbig; Güralp O. Ceyhan, MD; Markus W. Büchler, MD
Several pancreatic tumor entities and the extent of surgical radicality require a total pancreatectomy (TP). In the present study we report early and late outcome in 147 patients who underwent TP. Except for endocrine insufficiency, TP provides functional outcome and quality of life comparable to that of the pylorus-preserving Whipple procedure, as shown by matched-pairs analysis.

Unilateral Versus Bilateral Neck Exploration for Primary Hyperparathyroidism: Five-Year Follow-up of a Randomized Controlled Trial.
Johan Westerdahl, MD, PhD; Anders Bergenfelz, MD, PhD
In a prospective randomized trial for the surgical treatment of primary hyperparathyroidism, unilateral neck exploration with intraoperative parathyroid hormone assessment was found to be a valid surgical strategy with the same long-term results as bilateral neck exploration.
**Improved Kidney Graft Function After Preservation Using a Novel Hypothermic Machine Perfusion Device.**
Mark-Hugo J. Maathuis, MD; Steffen Manekeller, MD; Arjan van der Plaats, MSc, PhD; Henri G. D. Leuvenink, PhD; Nils A. ‘t Hart, MD, PhD; A Bastiaan Lier, MSc; Gerhard Rakhorst, DVM, PhD; Rutger J. Ploeg, MD, PhD; Thomas Minor, MD, PhD

Hypothermic machine perfusion using the Groningen Machine Perfusion system reduces ischemia reperfusion injury of porcine kidneys in an autotransplantation model. Compared with static cold storage less oxidative stress, less injury to proximal tubules and better kidney function were observed. Perfusion pressures during hypothermic machine preservation are, however, critically important for outcome.

**Extended Transthoracic Resection Compared With Limited Transhiatal Resection for Adenocarcinoma of the Mid/Distal Esophagus: Five-Year Survival of a Randomized Clinical Trial.**
Jikke M. T. Omloo, MD; Sjoerd M. Lagarde, MD; Jan B. F. Hulscher, MD; Johannes B. Reitsma, MD, PhD; Paul Fockens, MD, PhD; Herman van Dekken, MD, PhD; Fiebo J. W. ten Kate, MD; Huug Obertop, MD; Hugo W. Tilanus, MD, PhD; J Jan B. van Lanschot, MD

A randomized clinical trial was performed to compare extended transthoracic esophagectomy for adenocarcinoma of the mid/distal esophagus to limited transhiatal esophagectomy. Long-term survival data show an ongoing trend indicating a benefit for patients with type I esophageal tumors and patients with limited number of positive nodes if operated via the transthoracic approach.

**Mortality After Bariatric Surgery: Analysis of 13,871 Morbidly Obese Patients From a National Registry.**
Mario Morino, MD; Mauro Toppino, MD; Pietro Forestieri, MD; Luigi Angrisani, MD; Marco Ettore Allaix, MD; Nicola Scopinaro, MD, FACS Hon

The analysis of a large national prospective database on bariatric surgery demonstrated a 0.25% early mortality rate after bariatric surgery. Mortality was influenced by different risk factors, including type of surgery, open surgery, prolonged operative time, comorbidities, and hospital volume of activity. Choice of procedure, prevention, early diagnosis, and therapy for cardiovascular complications may reduce postoperative mortality.

**Open Right Colectomy Is Still Effective Compared to Laparoscopy: Results of a Randomized Trial.**
Marco Braga, MD; Matteo Frasson, MD; Andrea Vignali, MD; Walter Zuliani, MD; Valerio Di Carlo, MD

Postoperative outcome and hospital costs of laparoscopic versus open right colectomy were assessed in 226 randomized patients. Laparoscopic right colectomy resulted in an earlier postoperative recovery, whereas morbidity rate and quality of life were similar to open procedure. Because the cost-benefit analysis showed a relevant additional charge in the LPS group, open approach still remains an effective procedure.
**Randomized Controlled Trial**

1016 **Randomized Trial of Argon Plasma Coagulation Versus Endoscopic Surveillance for Barrett Esophagus After Antireflux Surgery: Late Results.**

Tim Bright, MBBS, FRACS; David I. Watson, MD, FRACS; William Tam, PhD, FRACP; Philip A. Game, MBBS, FRCS, FRACS; David Astill, PhD, FRCPath; Roger Ackroyd, MD, FRCS, FRCSEd; Bas P. L. Wijnhoven, MD, PhD; Peter G. Devitt, MS, FRCS, FRACS; Mark N. Schoeman, PhD, FRACP

This study reports 5-year results from a randomized trial of argon plasma coagulation versus surveillance for Barrett esophagus in patients who had undergone a fundoplication. Regression of Barrett esophagus was more likely after ablation, and in most patients the neosquamous mucosa was stable at late follow-up.

**Original Articles**

1021 **Laparoscopic Surgery Is Associated With a Lower Incidence of Venous Thromboembolism Compared With Open Surgery.**

Ninh T. Nguyen, MD; Marcelo W. Hinojosa, MD; Christine Fayad, BS; Esteban Varela, MD, MPH; Viken Konyalian, MD; Michael J. Stamos, MD; Samuel E. Wilson, MD

This study examined the incidence of venous thromboembolism (VTE) in patients who underwent open or laparoscopic appendectomy, cholecystectomy, antireflux surgery, and gastric bypass using a national database of academic centers. Overall, the incidence of VTE was significantly higher in open compared with laparoscopic cases (0.59% vs. 0.28%, respectively, P < 0.01). The findings from this study can provide a basis to help surgeons estimate the risk of VTE and implement appropriate prophylaxis for patients undergoing laparoscopic surgical procedures.

1028 **Substantial Intentional Weight Loss and Mortality in the Severely Obese.**

Anna Peeters, PhD; Paul E. O’Brien, MBBS, PhD; Cheryl Laurie, BHS; Margaret Anderson, BHIM, Grad Dip HA; Rory Wolfe, PhD; David Flum, PhD; Robert J. MacInnis, PhD; Dallas R. English, PhD; John Dixon, MBBS, PhD

We compared all cause mortality in a surgical weight loss cohort, treated with a laparoscopic adjustable band, to a similarly aged, obese population cohort. Weight loss patients had 72% lower hazard of death than the community control cohort (hazard ratio, 0.28; 95% confidence interval, 0.10-0.85).

1034 **Predictive Factors of Outcome After Gastric Banding: A Nationwide Survey on the Role of Center Activity and Patients’ Behavior.**

Jean-Marc Chevallier, MD, PhD; Michel Païta, MD; Marie-Hélène Rodde-Dunet, MD; Michel Marty, MD; Françoise Nogues, MD; Kareem Slim, MD; Arnaud Basdevant, MD, PhD

A systematic nationwide study on the 2-year outcome of all 1236 bariatric operations performed in France in December 2002 and January 2003 was conducted by independent consultants of the French National Medical Insurance Service. Statistical analysis identified a typical profile of success after gastric banding: patient younger than 40, initial body mass index below 50 kg/m2, willing to change eating habits, recovering physical activity after operation, and operated on by a surgical team performing >2 bariatric operations per week.
Prognostic Significance of Multiple Molecular Markers for Patients With Stage II Colorectal Cancer Undergoing Curative Resection.
Yih-Huei Uen, MD; Shiu-Ru Lin, PhD; Deng-Chyang Wu, MD, PhD; Yu-Chung Su, MD; Jeng-Yih Wu, MD; Tian-Lu Cheng, PhD; Chin-Wen Chi, MD; Jaw-Yuan Wang, MD, PhD

A membrane-array method was used for the detection of molecular markers in peripheral blood collected from stage II colorectal cancer patients. Our findings suggest that the presence of circulating tumor cell-related molecules is a poor prognostic factor for stage II colorectal cancer patients, with a high risk of postoperative relapse.

Inflammation-Based Prognostic Score Is a Novel Predictor of Postoperative Outcome in Patients With Colorectal Cancer.
Mitsuru Ishizuka, MD; Hitoshi Nagata, MD; Kazutoshi Takagi, MD; Toru Horie, MD; Keiichi Kubota, MD

Preoperative evaluation of Glasgow prognostic score, an inflammation-based prognostic score that includes simply C-reactive protein and albumin, is considered to be a useful predictor of postoperative mortality in patients with colorectal cancer.

Surgical Approach to Bismuth Type I and II Hilar Cholangiocarcinomas: Audit of 54 Consecutive Cases.
Takashi Ikeyama, MD; Masato Nagino, MD; Koji Oda, MD; Tomoki Ebata, MD; Hideki Nishio, MD; Yuji Nimura, MD

Records of 54 patients who underwent resection of a Bismuth type I or II hilar cholangiocarcinoma were analyzed retrospectively. Surgical strategy should be based on the cholangiographic tumor type. For nodular and infiltrating tumors, right hepatectomy is essential for cure; for papillary tumors, bile duct resection with or without limited hepatectomy is sufficient.

Fatty Pancreas: A Factor in Postoperative Pancreatic Fistula.
Abhishek Mathur, MD; Henry A. Pitt, MD; Megan Marine, MD; Romil Saxena, MD; C Max Schmidt, MD; Thomas J. Howard, MD; Attila Nakeeb, MD; Nicholas J. Zyromski, MD; Keith D. Lillemoe, MD

Surgical pathology specimens from the pancreatic neck of patients with and without a pancreatic fistula after pancreateoduodenectomy were examined for fat, inflammation, fibrosis, and vessel density. Patients with a pancreatic fistula had significantly more fat (P < 0.001) at the resection margin. We conclude that fatty pancreas is a risk factor for postoperative pancreatic fistula.

Right Hepatic Trisectionectomy for Hepatobiliary Diseases: Results and an Appraisal of Its Current Role.
Karim J. Halazun, MRCS; Ahmed Al-Mukhtar, FRCS; Amer Aldouri, MRCS; Hassan Z. Malik, MD, FRCS; Magdy S. Attia, MD, MS, FRCS; K Rajendra Prasad, MS, FRCS; Giles J. Toogood, DM, FRCS; J Peter A. Lodge, MD, FRCS

Short- and long-term outcomes of 275 consecutive patients who underwent right hepatic trisectionectomy from January 1993 to January 2006 are presented. One-, 2-, 5-, and 10-year survivals were 74%, 54%, 43%, and 36%, respectively. Age more than 70 years, preoperative bilirubin levels, and the development of postoperative renal failure were independent predictors of long-term survival.
1075 **Is Total Parathyroidectomy the Treatment of Choice for Hyperparathyroidism in Multiple Endocrine Neoplasia Type 1?**
Francesco Tonelli, MD; Tommaso Marcucci, MD; Geri Fratini, MD; Maria Silvia Tommasi, MD; Alberto Falchetti, MD; Maria Luisa Brandi, MD, PhD

The gold standard surgical approach to multiple endocrine neoplasia type 1-hyperparathyroidism (MEN1-HPT) remains elusive. In this report, we describe 51 cases of MEN1-HPT treated during 16 years of experience by the same operator using intraoperative parathyroid hormone monitoring and total parathyroidectomy with fresh tissue autograft. The results obtained support the use of this surgical procedure in MEN1-HPT.

1083 **Racial Disparities in Clinical and Economic Outcomes From Thyroidectomy.**
Julie Ann Sosa, MA, MD; Pritesh J. Mehta, BA; Tracy S. Wang, MD, MPH; Heather L. Yeo, MD; Sanziana A. Roman, MD

Clinical and economic outcomes from thyroidectomy were examined by race using Health Care Utilization Project National Inpatient Sample. Minority patients had more costly and longer hospital stays after adjusting for other variables. They underwent thyroidectomy by less experienced surgeons, suggesting inequity in access to care.

1092 **The Optimal Timing of Intestinal Transplantation for Children With Intestinal Failure: A Markov Analysis.**
Steven R. Lopushinsky, MD, MSc; Robert A. Fowler, MD, MSc; Girish S. Kulkarni, MD; Annie H. Fecteau, MD, MSc; David R. Grant, MD; Paul W. Wales, MD, MSc

The timing of intestinal transplantation in patients with intestinal failure is controversial. In this study, a Markov model was developed to compare early listing for intestinal transplantation against standard care, consisting of parenteral nutrition (PN) and delayed transplantation if necessary. Intestinal transplantation has reached a state of clinical equipoise with PN, and quality of life should be considered in the timing decision for transplantation.

1100 **The Michigan Surgical Quality Collaborative: Will a Statewide Quality Improvement Initiative Pay for Itself?**
Michael J. Englesbe, MD; Justin B. Dimick, MD, MPH; Christopher J. Sonnenday, MD, MHS; David A. Share, MD, MPH; Darrell A. Campbell Jr, MD

In this article, we detail a unique collaboration between hospitals in Michigan and a major third party payer, using a pay for participation model. The framework of this program should be used by surgeons to attract private payers into QI collaboratives, facilitating improved patient outcomes and decreased health care expenditures.

1104 **The Quality of Trials in Operative Surgery.**
Catherine J. Walter, MB, ChB (Hons); Jo C. Durville, PhD; Catherine E. Hewitt, MSc; Katie C. Moore, MB, ChB; David J. Torgerson, PhD; Philip J. Drew, MD; John R. T. Monson, MD

This study aimed to assess the quality of reporting seen in surgical trials. Surgical and nonsurgical trial methodologies were assessed against predefined criteria, and the results were compared. There was no evidence that the reported quality of surgical trials differed from nonsurgical trials, with about half of all trials reviewed reporting adequate methodology.
Little Science, Big Science: Strategies for Research Portfolio Selection in Academic Surgery Departments.

Anand Shah, BS; Ricardo Pietrobon, MD, PhD, MBA; Chad Cook, PT, PhD, MBA; Neil P. Sheth, MD; Lam Nguyen, BS; Lucie Guo, BS; Danny O. Jacobs, MD, MPH; Paul C. Kuo, MD, MBA

We evaluated National Institutes of Health funding data from 2002 to 2004 for academic surgery departments and determined whether optimal portfolio strategies exist to maximize this funding. Our findings suggest that the best strategy is to invest in individuals with focused research commitments and established track records of garnering large and multiple research grants.

Letters to the Editor

Prophylactic Ilioinguinal Neurectomy in Open Inguinal Hernia Repair: A Double-blind Randomized Controlled Trial.

Johan F. M. Lange, MD; Arthur Wijsmuller, Resident, Surgery; Dick van Geldere, MD

Does a Biologic Prosthesis Really Reduce Recurrence After Laparoscopic Paraesophageal Hernia Repair?

Thomas W. Rice, MD; Eugene H. Blackstone, MD

Does a Biologic Prosthesis Really Reduce Recurrence After Laparoscopic Paraesophageal Hernia Repair?

Brant Oelschlager, MD; Carlos Pellegrini, MD; James Nelson, MD; Lee Mitsumori; John Hunter, MD; Brett Sheppard, MD; Blair Jobe, MD; Nathaniel Soper, MD; Michael Brunt, MD; Nayak Pollisar, PhD; Lee Swanstrom, MD

Mental Training in Surgical Education.

Sourabh Mukherjee, MD

Mental Training in Surgical Education.

Marc Immenroth, PhD; Thomas Bürger; Jürgen Brenner, MD; Manfred Nagelschmidt, PhD; Hans Troidl, MD; Hans Eberspächer, PhD
Why Should Young Doctors Choose to Become Surgeons?

Peter Neuhaus, MD, PhD

General surgery is the basis of all surgical specialties. It is the core of surgical education for young students and represents operative medicine for the population. Yet there has been a constant struggle over the last years in many western societies to attract enough of the best young medical students and motivate them to become surgeons. Statistics show that we are presently confronted with 3 problems regarding the recruitment of young surgeons:

1. The total number of medical students, especially those who have successfully completed their final examinations, has declined continuously during the last 12 years (Fig. 1).

2. General surgery as a profession is not as attractive as it once was. Hard training, long hours, late careers, little private life and flexibility, relatively poor income, and considerable physical demands are only a few arguments against a surgical career.

3. The percentage of students who opt for a career in research, the pharmaceutical industry, or in various other fields of the healthcare system without direct patient contact, and those who decide to work in a sector other than the medical field, is already as high as 25%.

In Germany the total number of practicing physicians under 35 years of age dropped during the last 15 years from 27% to 16% (Fig. 2), whereas the average age of physicians increased from 46 to 51 years.

This situation has become a real problem for surgery. Doctors working outside the hospital environment can usually work beyond 65 years of age, but this is an option that generally does not apply to hospital physicians and particularly not to surgeons.

Also, their freedom to make professional choices is rather limited. A change between hospital and medical practice, the combination of two different fields of interest or working in part-time surgery is difficult, especially for women. The chance to reduce the workload when general physical capability and performance decline due to age, injuries or disease is as well rather limited. Long working hours and night duties, physically demanding and stressful operations, the extremely high requirements for quality and the risk of error contribute to the problem. The retirement age of American surgeons has gone down from a mean of 71 to 57 years during the last 20 years.¹

The difficult situation in the United States is also highlighted by the fact that 10% of all surgical residency positions cannot be filled, and that during the last several years, surgical residents had to be continuously recruited from foreign countries. In 2002, Debas showed that the attractiveness of a career in general surgery decreased tremendously, whereas other surgical specialties were not confronted with this phenomenon.²

The list of investigations, alarming findings, explanations, and recommendations is long. Today it is of vital
importance to find ways to motivate young medical students and doctors to become surgeons.

One well established theory explaining personal motivation is Abraham Maslow's hierarchy of needs, published in 1954 with the title "Motivation and Personality." Maslow hypothesized that people are motivated by a hierarchy of needs (Fig. 3) such that:

Each individual's needs must be satisfied at a lower level before they progress to higher more complex levels. Also, when lower level needs are satisfied, individuals can no longer be motivated by them, they progress to higher level motivators, but all of their needs are always present.

Physical survival needs are expressed on the lowest level. The next level addresses the need for physical safety and security, freedom from threats, comfort, and peace.

Of course, medical students or young doctors generally do not have to worry about their physical security and safety needs, and so these basic low-level needs no longer motivate their actions. Today most academics and young doctors are motivated by social needs, self-esteem needs, and self-actualization needs. In an investigation of young American surgeons asked to give reasons for their choice of profession, most ranked personal drive and motivation for a surgical career much higher than anticipated lifestyle, length of training, and financial issues.

Here, one must, however, bear in mind that the income of American doctors is considerably higher than that of European hospital doctors, especially those in Denmark, Sweden, Germany, and Spain (Fig. 4).

After basic needs are satisfied, Maslow contends that individuals begin to look for a sense of community and fulfillment of their needs for belonging and love. These needs include desire for family and greater satisfaction in work relationship or social structures. It is important that the social structure provides an individual the ability to give and receive affection. Young surgeons are recruited on this level of needs (Fig. 3).

To meet these needs and to create enthusiasm for surgery means to offer young surgeons a positive view of surgery and a place in a surgical community that not only fulfills their basic needs, but also creates the sense that they can achieve an accepted and recognized position within this group. Recognition from other medical students, friends, family, nurses and colleagues, senior surgeons and finally also from patients, generates the basic feeling of success and satisfaction. Parallel to this, the social prestige and recognition of one's own achievements or strength increases much as is also seen in sport activities. Therefore, reputation, prestige, and status are important motivators for surgeons; disruptions, on the other hand, are often reasons for frustration and resignation.

According to a current survey, German medical students are motivated during their final year of clinical education by practical clinical work (96%), responsibility for individual patients (90%), engagement of senior surgeons (81%), continuous cooperation with and learning from older surgeons (64%), a surgical mentor guide and role model (80%),

FIGURE 3. Maslow's hierarchy of needs, 1954. Each individual's needs must be satisfied at the lower levels before they progress to higher and more complex levels.3

FIGURE 4. Hospital doctor's annual average earnings, 2002. The bars represent the highest average annual earnings estimate in US (equalized to purchasing power) in different countries.5
and less pressure and stress (64%).6 Many students associate a career in general surgery with irregular schedules, limited family and leisure time, and a high level of stress. Control over lifestyle and manageable working hours are important. Income, however, is not as important. Surgeons are regarded as having unique academic and career opportunities, prestige through highly developed skills, and a sense of accomplishment as well as exposure to intellectual challenges.7

By offering positive role models, surgeons can increase the possibility that students will pursue a surgical career. Attending surgeons may increase students’ motivation by expressing their surgical and nonsurgical interests and discussing these with students during preclinical and clinical teaching. Students can, for instance, spend a day in surgery with the surgeon, or for example, join the operating room with a faculty member. They can engage in interesting and motivating surgical tasks like organ donation and transplantation. They can also be involved in experimental research and in clinical investigations, or in small jobs within the clinic. Surgical operative courses and computer assisted or laparoscopic surgery training is also popular among students. There may be opportunities to participate in experimental animal surgery and other bench models for surgical training to build commitment and a feeling of surgical dexterity. Student or young resident exchange programs, like the Erasmus program,8 invitations to surgical clinical conferences, and small local symposia may also increase acceptance and identification.

Senior surgeons should show interest in and commitment to addressing the following points:

- Aspects of education such as specialization and future career should be discussed more often and in a friendly manner.
- The combination of work and family must be discussed, especially with female students, and good mentorship is also very important.
- During the early phase of a young surgeon’s career, he or she should be included in a team whose members provide support according to his/her abilities.
- Social and private contacts like sports activities may also create positive feelings and the desire to be part of the team.

Motivation is lost when basic needs are at risk. This means having an adequate salary, job security, and contentment, which includes leisure time, time for friends, cultural events, relaxation, sport, and hobbies. Motivation is lost if one’s work is unsatisfactory, surgical education is unstructured, and if there are conflicts and tension within one’s group. Motivation can also be diminished by poor role models. When 50% of surgeons over the age of 50 years have major health problems and 7% have alcohol problems,9 the positive image of surgery is damaged. Indifference, cynicism, sarcasm, depression with diminished self-esteem, bad temper, mistrust, impatience, and a feeling of emptiness are possible symptoms of a lack of personal freedom, too many responsibilities, the need to treat too many patients, or too much administrative and economic control. As a consequence of stress and excessive demands on older doctors, especially surgeons, “burnout-syndrome” may negatively influence the career choice of young doctors, because they regard older colleagues as their role models.10

As an example, the quotation: “I have done too much, for too many, for too long with too little regard for myself,” is a reflection that the increasing demands of our healthcare systems are paid for mostly by the doctors and discourages young medical students.11

The desire to be accepted and involved in a successful team and to receive real love and affection, professionally as well as privately, is somewhat in contradistinction to our earlier perception of a surgical role model, where the surgeon is God, alone and almighty, but uncontrolled, uncooperative, and despotic, as mentioned in Krister HÖckerstedt’s 2006 presidential address.12

Today this role model is not attractive anymore, instead we look for the listening and motivational team leader, who stands out by his exceptional knowledge and capabilities and earns his professional authority. At the same time, this person should be friendly, helpful and unselfish, and should acknowledge that he is not all-knowing and cannot do everything better. Other team members may also be competent and, consequently, some responsibilities will be transferred to those people, something that we now call team work and low hierarchy (Fig. 5). Such team structures will, on the basis of our societal and cultural perceptions, be valued by young surgeons contrary to a hierarchic structure. It can also help prevent subjective and objective errors and anxieties, and can add toward greater satisfaction on all levels of surgical work.

This brings us automatically to the next level of Maslow’s hierarchy of needs, namely the need for self-esteem (Fig. 3). In addition to being accepted, people want to be heard and appreciated. They want their intelligence, strength, and skills to be recognized. In particular, young surgeons want to feel important and to develop prestige and status.

Young doctors, especially those with enthusiasm for surgery, are not discouraged by high demands, but these demands must be structured, visible, goal oriented, and achievable. We all agree that surgical education is the touchstone for young doctors regarding their professional choices. Young doctors, who are interested in a surgical career,
demand a clear structured educational curriculum. They want to receive coaching and mentorship from senior surgeons and department heads. They also want to be part of a team, which does not allow a high dropout rate because of excessive competition. A too high workload and too much pressure for an optimal and error-free performance in hospital and society can discourage young people who will look for simpler solutions outside of surgery.

The ultimate goal of becoming a respected surgeon, to treat patients at a highly skilled level, to look for new avenues and interesting solutions of medical problems, to meet individual challenges, and to gain respect and prestige, must not be disturbed by adverse factors. These include the never-ending and unsatisfactory obligations in documentation and administrative demands, stress from too many important obligations that could be delegated, and frustration created by structural deficiencies in the teaching clinic.

The thrilling discussion and teaching of new therapeutic modalities, the fields of research and interesting scientific findings always carry a very special attraction for students. In this regard, I personally like to remember the early years of clinical transplantation surgery, when I, as a student at the Glasgow Royal Infirmary in 1970, participated and assisted in experimental lung transplantations. The newly developing field of organ transplantation fascinated me as a medical student and I have never turned away from this field. In addition, I was very lucky to find Rudolf Pichlmayr in Hanover as my surgical role model, who as a surgeon at that time embodied everything that we wish for and demand of a surgical leader today. I was proud to become part of his surgical team and participate in this difficult and at that time unforeseeably successful experimental and clinical liver transplantation project.

Since then many new fields of surgery have developed that spark an interest and enthusiasm and input from young surgeons. In addition to liver transplantation, we have seen the development of heart transplantation, the artificial heart, osteosynthesis in trauma surgery and orthopedics, as well as the development of minimally invasive and robot-assisted procedures in visceral surgery, to name only a few. Scientific discoveries in molecular biology, genetics, temporary organ support and organ replacement, intensive care medicine, immunology, and oncology allowed for better understanding of complex medical problems and new therapies for life-threatening diseases.

Surgical diseases are now not only treated in an interdisciplinary context, but under special circumstances, more and more without surgery. Here, we encounter a new problem for surgery, which is important and must be addressed. Surgical operations are replaced by endoscopic procedures or interventional radiology. Drug treatment instead of surgery has become successful, for conditions such as gastroduodenal ulcers.

Medical students may be attracted to or put off by surgery depending on who they learn from. For example, whether a gastroenterologist or a surgeon presents a lecture about diseases of the alimentary tract may influence how students feel about surgery. Unfortunately, we have to realize, that at least in Germany, surgeons are often replaced by internists teaching the students in medical school, as a consequence of a too heavy workload in the clinic. This fact is, however, more or less accepted by surgeons without resistance. Here, the attractiveness of a surgical career is already diminished in medical school.

At the same time, the erroneous impression is given that it is internal medicine and not surgery that provides the true progress in medicine. Visibly important and well conducted clinical trials including multimodal approaches, for instance in cancer therapy, conducted in a surgical unit, are most convincing for young students when they make their career choices.

Also the decreasing number of experimental studies in our surgical labs and the increasing number of biochemical genomic and proteomic research projects, as well as the lower rating of surgical science when compared with other scientific fields, measurable as low-impact factors for surgical journals, play an important role. These tendencies must be acknowledged. It is necessary through the positive active role of surgical leaders to picture surgery as a field with high scientific goals and great prospects.

Returning to Maslow’s hierarchy of needs and the need for self-esteem (Fig. 3), prestige and status are important factors in an individual’s choice of profession. As Krister Höckerstedt said, “Surgery still is one of the most appreciated professions.” He quoted a survey that was performed regularly since 1971. Nevertheless, surgeons feel the disturbance in their professional autonomy by guidelines and administrative rules. Also, there is a general feeling among surgeons that increasing demands from society for information and in decision-making challenged their surgical prestige, acceptance, and recognition.

Generally we know that a functioning administration, a good professional organization, a good working climate, good cooperation among colleagues, and a level of autonomy lead to greater satisfaction in the workplace. Moreover, an adequate fixed remuneration package depending on the qualifications and performance is important. This is specifically true in surgery, since nowhere else are performance and quality so obviously visible. Job satisfaction can be lost when these conditions are ignored, especially when significant pressure on performance, quality and efficiency together with restrictions of resources, and operational freedom are imposed.

The unique value of the patient-doctor relationship separates surgery from other professions. Individual treatment and individual decision-making are at risk from the increasing economical needs of our healthcare system, with continuously rising pressure from health insurance companies and hospitals on surgical decisions. This places the head of the surgical department in a key position. It is his responsibility to assign important projects to coworkers and to recognize their strengths and intelligence. Leadership in interdisciplinary clinical working groups and in surgical research groups underlines his internal reputation. The leading role of surgery in multidisciplinary teams and centers bears recognition and importance beyond specialty borders and at the same time generates prestige and social status, which in turn attracts young doctors.
According to Maslow, the fulfillment of one’s needs for recognition serves as a preparation to climb the highest step of the hierarchy of needs, and is associated with new demands for the surgical leader to become a role model. In his need for self-actualization, his readiness and competence to learn and teach, he gains in significance apart from his personal, clinical, and scientific reputation. The changes in our health system and in our surgical field are constantly paired with great challenges and open new opportunities to make use of new scientific results in a creative manner without disregard to past achievements.

The chairman’s own needs lift his coworkers onto the next level of the hierarchy of needs and open new perspectives in an otherwise too conservative system of surgery. According to Maslow, the highest level in his hierarchy of needs is reached by finding self-fulfillment and realizing one’s own potential. On the cognitive level this means to know, to understand, and to be able to explore. On the esthetic level one strives for symmetry, order, and beauty. Ultimately, approaching self-transcendence one helps others to find self-fulfillment and to realize their potential. People at this stage seek information on how to promote others.

Daniels in 2001 suggested that Maslow’s ultimate conclusion, that the highest level of self-actualization is transcendent in nature, may be one of his most important contributions to the study of human behavior and motivation.¹³

**CONCLUSIONS**

There are ways we surgeons can influence medical students’ and young doctors’ decisions toward a surgical career if we meet certain requirements.

In this regard, it is useful to consider Abraham Maslow’s hierarchy of needs and focus primarily on social needs. This means we must care for young surgeon with:

- Improved working conditions (controllable lifestyle)
- A family friendly environment
- Better surgical education
- Higher pay
- Good academic and career opportunities

We should then more actively recruit or interest young students and doctors in surgical education through early exposure to interesting surgical fields, participation in surgical teamwork, practice in surgery and laboratory training courses, and preparation to serve as tutors and mentors for students.

At the same time, we can offer a bright picture for the future surgeon’s life as Henry Debas said in his 2002 American Surgical Association presidential address, “This is a noble profession in a changing world.” And, as Krister Höckerstedt said in 2006, surgery is still first among the most appreciated professions.¹²

Surgery conveys a feeling of competence, skill and expertise, and offers exposure to intellectual challenges. Prestige and financial reward may compensate for a great deal of extra work and inconvenience. Surgeons also depend on trust and respect, and sometimes even admiration and love, and, therefore, surgeons are taller and better looking than physicians.¹⁴

**REFERENCES**

Long-term Results of Intersphincteric Resection for Low Rectal Cancer

Reza Chamlou, MD,* Yann Parc, MD, PhD,* Tabassome Simon, MD, PhD,† Malika Bennis, MD,* Nidal Dehni, MD,‡ Rolland Parc, MD,* and Emmanuel Tiret, MD*

Introduction: In the treatment of very low rectal cancer, a distal resection margin of more than 1 cm can be obtained by partial internal sphincter resection, allowing a sphincter preserving surgery. Thus, intersphincteric resection (ISR) has been proposed as an alternative to abdominoperineal resection for selected low rectal cancer.

Objective: The aim of our study was to assess the morbidity, mortality, and the long-term oncologic and functional results of ISR.

Methods: Charts of patients who had ISR between 1992 and 2004 were reviewed. Cancer-related survival and locoregional recurrence rates were calculated using the Kaplan–Meier method. Functional outcome was assessed by using a standardized gastrointestinal functional questionnaire. Incontinence was assessed by the continence score of Wexner.

Results: Ninety patients (59 males, 31 females) with a tumor at a median distance of 35 mm (range, 22–52) from the anal verge had an ISR. Thirty-seven patients (41%) had preoperative radiotherapy.

Histologically complete remission after neoadjuvant radiotherapy (ypT0) was observed in 7 patients (8%), 12 patients (13%) were pT1, 35 patients (39%) pT2, 32 patients (36%) pT3, and 4 patients (4%) pT4. Five patients (5.5%) had synchronous liver metastases. R0 resection was obtained in 85 patients (94.4%). The median distal resection margin on the fixed specimen was 12 mm (range, 5–35) and was positive in 1 case. The circumferential margin was positive (≥1 mm) in 4 patients (4.4%). There was no mortality. Complication rate was 18.8%: anastomotic leakage occurred in 8 patients (8.8%) and 1 patient had an anovaginal fistula. Five patients (5.6%) underwent secondary abdominoperineal resection: 1 for positive distal margin, 1 for colonic J-pouch necrosis, and 3 for local recurrence.

Oncologic Results: After a median follow-up of 56.2 months (range, 13.3–168.4), local, distant, and combined recurrence occurred in 6 (6.6%), 8 (8.8%), and 2 patients, respectively. Thirteen patients (14.4%) died of cancer recurrence. Five-year overall and disease-free survival was 82% (80–97) and 75% (64–86), respectively. In univariate analysis, overall survival was significantly influenced by pTNM stage and T stage (pT 1–2 vs. 3–4: P = 0.008 and stage I–II vs. III–IV: P = 0.03). In multivariate analysis, we did not find any impact on local recurrence-free survival for the investigated prognostic variables.

Functional Results: For a total of 83 patients the mean stool frequency was 2.3 ± 1.3 per 24 hours. Forty-one percent of patients had stool fragmentation, one-third nocturnal defecation, 19% fecal urgency, and 36% followed low fiber diet. Thirty-four patients (41%) were fully continent, 29 patients (35%) had minor continence problems, and 20 patients (24%) were incontinent. After adjustment for age, gender, tumor level, and pTNM stage, preoperative radiotherapy was the only factor associated with a risk of fecal incontinence [OR (IC 95%) = 3.1 (1.0–9.0), P = 0.04].

Conclusion: In selected patients, ISR is a safe operation with good oncologic results. It achieves good functional results in 76% of patients. Functional results are significantly altered by preoperative radiotherapy.

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T

reatment of rectal cancer has radically evolved during these last 30 years. Distal intramural spread of the tumor beyond 1 cm has been found to be infrequent and usually inferior to 1 cm. Reappraisal of the distal margin from 5 to 2 or even 1 cm has allowed increased in sphincter-saving resections without compromising oncologic results. For very low tumors, this necessary safe distal margin can only be achieved by resection of a variable part of the internal sphincter or by abdominoperineal resection. Intersphincteric resection (ISR) has been proposed to achieve distal clearance in some selected patients with very low rectal tumors extending to within 2 cm from the upper part of the sphincter. This technique described by Schiessel et al1 represents the most extreme form of sphincter resection and has been proposed as an alternative to abdominoperineal resection to reduce the number of patients requiring permanent colostomy.

However, partial resection or total resection of the internal anal sphincter can interfere with fecal continence. Before generalization of this operation, the questions of long-term oncologic results and functional outcome must be assessed in large series of patients. The principal objectives of this study were to report our results of ISR, especially with...
regard to the midterm oncologic and functional results. The secondary aim was to determine if there were some predictive factors of poor functional outcome.

METHODS

Charts of all patients with a biopsy-proven adenocarcinoma of the lower third of the rectum who required an ISR technique between January 1992 and December 2004 were reviewed. Staging evaluation included digital examination, colonoscopy with biopsy, anorectal ultrasonography, abdominal CT, and MRI in the most recent cases. Anorectal manometry was not routinely performed. Criteria for exclusion of ISR were invasion of external sphincter or levator ani, and patients not fully continent preoperatively. Patients with US T1 tumors were considered for transanal local excision. ISR was proposed to those patients with adverse pathologic features on the resected specimen.

Surgical Technique

The principle of the ISR technique is based on an anatomic dissection plane between the internal sphincter muscle, which is a prolongation of the muscular layer of the rectum, and the external sphincter. Surgical intervention was started first with the abdominal approach during which a high ligation of the inferior mesenteric vein was performed under the lower edge of pancreas. Then, division of the inferior mesenteric artery at 2 cm from its origin and division of the left colonic vessels was performed. This was followed by the mobilization of the splenic flexure. A standard TME was carried down to the levator ani plane and the anorectal junction. The intersphincteric plane was entered at the anorectal junction, and if possible, the intersphincteric dissection was performed until a sufficient distal margin was found. If this dissection was technically difficult by the abdominal approach, the transanal approach of the operation was then started, after perineal exposure with a retractor (Lone Star retractor, Lone Star Medical products Inc., Houston, TX). Mucosal and muscular incision was performed circumferentially at least 1 cm below the inferior extent of the tumor. If this incision was done at the pectinate line or 1 to 2 mm distally, the resection was considered to remove the upper half of the internal sphincter. If the resection was performed just above the pectinate line but below the anorectal junction, the resection was considered as upper third. A gauze with tumoricidal solution (betadine) was then inserted in the anal canal and the proximal rectum was closed transanally as soon as possible to reduce the risk of tumor-cell dissemination. Then, the dissection was pursued in the plane between the internal and external sphincter longitudinally to reach the abdominal dissection. The rectum was removed through the abdomen. A coloanal hand-sewn anastomosis with a colonic J-pouch was then performed. The anastomosis was protected with a diverting loop ileostomy reversed after 2 months.

R0 resection was defined by complete microscopic resection with circumferential margins >1 mm.

Follow-up

Patients were followed using a standardized protocol, including a clinical examination with digital palpation, abdominal and pelvic computed CT-scan, chest x-ray, and blood samples including tumors markers, every 4 months the first 2 years, then every 6 months for 2 more years, and then once a year. A total colonoscopy was performed 1 year after surgery and according to the presence of adenoma every year or 3 years after.

Endpoint Assessment

The endpoints of the study were local recurrence rate, survival and functional results. Local recurrence was defined as the presence of any anastomotic, pelvic, or perineal recurrence documented either by clinical or by pathologic examination.

Functional outcome was assessed using a standardized gastrointestinal functional questionnaire. In this questionnaire, patients were asked about stool frequency, fecal urgency, the need to wear a pad, stool fragmentation, nocturnal defecation, using of intestinal transit regulators, feces and flatus discrimination, and alimentary restrictions. Incontinence was assessed by the continence score of Jorge and Wexner.10

Statistical Analysis

Relationships between functional binary outcomes and surgical outcomes or radiotherapy were assessed with Pearson χ2 test or Fisher exact test when appropriate. A logistic regression model was assessed to investigate incontinence adjusted for age, gender, and tumor stage. Survival rates were assessed using Kaplan–Meier method. Potential prognostic factors were investigated using the logrank test. All test were 2 sided. The functional analysis was performed using SAS V9 System (SAS Institute, Cary, NC) and survival analysis using the R software [R Development Core Team (2004). R Foundation for Statistical Computing, Vienna, Austria, http://www.R-project.org].

RESULTS

Patient Characteristics

Ninety patients (59 males, 31 females) with a median age of 58.9 (range, 27–82) years had an ISR during the study period. They represented 6.8% of the 1319 patients operated on for rectal cancer in the same period. Thirty-seven patients (41%) had preoperative radiotherapy: 24 patients had long-course radiotherapy (45 Gy), followed by surgery 6 weeks later, and 13 patients had short-course radiotherapy (25 Gy), followed by surgery the week after. Nine patients (10%) had had a previous transanal resection, and ISR was decided because of high-risk pathologic features.

T4 tumors were not an exclusion criterion if the invasion of adjacent organ was distant from the lower part of the tumor and the sphincter, and was resectable. Four tumors had a resectable anterior extension, 3 of them to the posterior vaginal wall and one to the prostate. In all 4 of these cases the anterior extension was limited to the upper part of the tumor, which was distant from the sphincter. They had a synchronous partial posterior colpectomy and partial prostatectomy. Resectable distant metastases were not a criterion of exclu-
sion, and 5 patients (5.5%) had synchronous liver metastases and 1 had synchronous liver and lung metastases.

**Tumor Characteristics**

The median distance between the tumor and the anal verge was 35 mm (range, 22–52).

According to the UICC TNM classification, histologically complete remission after neoadjuvant radiotherapy (ypT0) was observed in 7 patients (8%). Twelve patients (13%) had a pT1 tumor, 35 patients (39%) a pT2, 32 patients (36%) a pT3, and 4 patients (4%) a pT4 tumor. Tumor was classified as stage 1 in 37 patients (41%), stage 2 in 16 patients (18%), stage 3 in 25 patients (28%), and stage 4 in 5 patients (6%).

**Surgical and Histologic Findings**

Level of internal sphincter resection was the upper third in 63 and the upper half in 27 patients. Complete microscopic resection (R0 resection) was obtained in 85 patients (94.4%).

The median distal resection margin on the fixed specimen was 12 mm (range, 5–35) and was positive in 1 patient who had then an immediate abdominoperineal resection. The circumferential margin was positive (≤1 mm) in 4 patients (4.4%) despite preoperative radiotherapy in 2 (1 short course and 1 long course). All underwent adjuvant treatment (3 had a chemotherapy and 1 postoperative radiochemotherapy).

**Mortality and Morbidity**

There was no mortality. Seventeen patients (18.8%) had at least 1 complication (Table 1). Anastomotic leakage occurred in 8 patients (8.8%).

One patient had a vaginal fistula, which eventually healed after salvage surgery with a new coloanal anastomosis 5 months after initial surgery. In 5 patients, anastomotic leakage was associated with a pelvic abscess which was evacuated by a CT-guided drainage in 3 cases and surgically in 2 cases. Ileostomy was closed in these 5 patients after 3 months (range, 2–5 months). In the remaining 2 patients, anastomotic leakage was observed in radiographic control before closure of the stoma. They were treated conservatively, and fistula was closed spontaneously by delay of stoma closure. The ileostomy was then reversed in 1 after 2 and in the second after 3 months. One patient had a J-pouch necrosis and required an emergency APR.

**Oncologic Results**

After a median follow-up of 56.2 months (range, 13.3–168.4), local, distant, and combined recurrence occurred in 6 (6.6%), 8 (8.8%), and 2 patients, respectively.

Liver metastases occurred in 3 patients, pulmonary metastases in 5 patients and combined liver and pulmonary metastases in 2 patients. Thirteen patients (14.4%) died of cancer recurrence.

Median disease-free interval for the 6 patients with local recurrence was 13 (range, 6–44) months. Five of the 6 isolated local recurrences developed within the first 3 years and the last one occurred after 44 months. Four of the 6 were female, and the average age at the time of recurrence was 65 years (range, 47–84) years. Histopathologic grading was well differentiated in 4 and moderately differentiated in 2 patients. The median distal resection margin was 6 (range, 5–30) mm (Table 2). Among the 8 patients with local recurrences, 5 (62.5%) had a distal resection margin ≤1 cm. In 1 patient, the

<table>
<thead>
<tr>
<th>TABLE 1. Postoperative Complications</th>
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<tbody>
<tr>
<td>Anastomotic leakage</td>
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<tr>
<td>Pelvic hematoma</td>
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<td>Partial wound dehiscence</td>
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<td>Small bowel obstruction</td>
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<td>Upper Gl bleeding</td>
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<td>Septicemia</td>
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<td>Pouch necrosis</td>
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<td>Acute pancreatitis</td>
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<td>Pulmonary embolism</td>
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<tr>
<th>TABLE 2. Characteristics of 6 Patients With Local Recurrence and 2 Patients With Combined Recurrence</th>
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<td>Patient</td>
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APR indicates abdominoperineal resection; PE, pelvic exenteration.
circumferential margin was positive. This patient had a neo-
adjuvant radiochemotherapy. Three patients who developed
local recurrence had an APR for treatment of their local
recurrence (1 of them was combined with a total pelvic
exenteration because of prostatic invasion).

Five-year overall and disease-free survival was 82%
(range, 80–97%) and 75% (range, 64–86%), respectively
(Figs. 1 and 2). In univariate analysis, overall survival was
significantly influenced by pTNM stage and T stage (pT 1–2
vs. 3–4: P = 0.008 and stage I–II vs. III–IV: P = 0.03). In
multivariate analysis, we did not find any impact on local
recurrence-free survival for the investigated prognostic vari-
ables (ie, sex, age, size of the tumor, tumor distance to the
anal verge, pT stage, tumor stage, lateral margin, distal
margin, and preoperative radiotherapy).

**Functional Results**

Functional results were assessed on 83 patients at
follow-up (2 lost to follow-up and 5 abdominoperineal resec-
tion), and are shown in Table 3. According to the Wexner
score, 34 patients (41%) were fully continent (Wexner score = 0), 29 patients (35%) had an acceptable function with
minor continence problems (mean Wexner score = 3.7), and
20 patients (24%) were incontinent with a mean Wexner
score of 15. Among this latter group, 2 were totally inconti-
ent. These 2 patients did not wish to permanent stoma.
Overall, 76% of patients were satisfied with the functional
results of surgery.

Table 4 shows the results of continence according to
gender, preoperative radiotherapy, level of internal sphinc-
ter resection, pTNM, and tumor stage. Only preoperative radio-
therapy had a significant impact on the functional outcome at
univariate analysis. This was confirmed on multivariate anal-
ysis, after adjustment for age, gender, and pTNM stage
[OR (IC 95%) = 3.1 (1.0–9.0), P = 0.04] (Table 5).

**DISCUSSION**

This study reports the results of a series of 90 consec-
tive patients having undergone ISR for low rectal cancer
between 2 and 5 cm from the anal margin, with a median
follow-up of 56 months. Our data show that this operation is
feasible and safe, with no postoperative mortality and accept-
able morbidity. A complication occurred in 17 (18.8%) pa-
tients, and anastomotic leakage occurred in 8% of patients,
inferior but not significantly different to the 11.5% reported in
our initial experience of ISR. Only 1 patient had a permanent
stoma due to a postoperative complication. These data are in
keeping with other large series of ISR reported in the literature,
with low postoperative mortality between 0% and 0.8% and
morbidity rate between 7.7% and 27%.5,8,9,11,14,15

Including the 2 patients who had a combined recur-
rence, 8 patients had a local recurrence. The overall local
recurrence rate was 8.8% higher than the 3% rate that we
reported on the first 26 patients.7 Details for these 8 patients
are given in Table 2. One patient had a likely implant of
malignant cells on an hemorroid and was cured by simple
hemorrhoidectomy. Four other patients had a stage 3 tumor
despite preoperative radiochemotherapy and it cannot be
assumed that a more extensive resection could have avoided
recurrence. The same observation can be made for distant
recurrence which occurred in 8% of the patients versus 0% in
the previous series, but the follow-up was only 30 months.
These results are again in keeping with the literature, with
local recurrence rates between 2% and 12.8%.5,9,14,15 They
are not very different from those of larger series of rectal
cancer in general, 16,17 operated with TME, indicating that ISR can achieve good local control, despite the low location of the tumor and the technical challenge to obtain the necessary safe distal margin. However, it must be underlined that this operation is not suitable for every low rectal cancer. Preoperative assessment and particularly rectal endosonography are important to select those patients who have a tumor confined to the rectal wall at least in its distal part, close to the sphincter. More than half (52%) of the patients of our series had a T1 or T2 tumor. The percentage of tumors limited to the rectal wall ranges between 50% and 68% in most series of ISR in the literature. With the exception of the series of Rullier et al15, in which T1–T2 were only 14%, this rate of T1–T2 tumors is higher than in series of rectal cancer in general, meaning that RIS has been performed in a selected population of patients, with a less invasive tumor. So, to validate the technique, recurrence rate and death from cancer of these less invasive tumors should at least not be superior to those of rectal cancer in general. This was achieved in this series with a 5-year overall survival and a disease-free survival of 82% and 75%. In the literature, most recent studies have reported an overall survival rate between 79% and 91.9% and a disease-free survival rate between 70% and 83.2%.4,5,9,14,15

For these very low tumors, transanal local excision should be considered for UST1 tumors, which has the benefit of a lower morbidity and preserves anorectal function. However, immediate radical surgery (ISR) should be advocated after local excision in case of adverse pathological features, like in 9 patients of this series. For T2 and more advanced tumors the alternative to ISR is abdominoperineal excision. We reported previously our oncologic results after APR with a LR rate of 5% and a 5-year-survival rate of 76%.18 Although there is no randomized study comparing these 2 techniques, Gamagami et al19 compared in a prospective study the LR rate and survival in patients with distal third rectal cancer treated either by coloanal anastomosis or APR. The LR rate was 7.9% after sphincter saving resection and 12.9% after APR. The 5-year actuarial survival rate was 78% after sphincter saving resection and 74% after APR.19 It can be concluded that when ISR is feasible, the oncologic prognosis is not compromised.

If ISR is technically feasible and oncologically safe, the next question that needs to be answered concerns the functional outcome after partial resection of the internal sphincter. This operation combines the side effects of a sphincteric resection with those of a low rectal resection, associating urgency, frequency, fragmentation of stools, and incontinence at various degrees. It has been shown that the addition of a colonic pouch can minimize this dysfunction,20–23 and all patients of this series had a pouch. The mean stool frequency per 24 hours was 2.3 ± 1.3 and was comparable to other series.8,14 Sixty percent of our patients had 2 or less bowel motions per day, and nocturnal defection occurred in one-third of the patients. Urgency was observed in 19%. This dysfunction is the consequence of the rectal resection. At follow-up, only 41% of the patients were fully continent, and another 35% experienced some minor incontinence, giving a 76% rate of patients who had a good or acceptable function were satisfied with the functional result. Among the 24% of patients with impaired continence, 2 were totally inconti-

<table>
<thead>
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<th>TABLE 3. Functional Results After ISR</th>
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<tbody>
<tr>
<td>Stool frequency per 24 h</td>
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<tr>
<td>≤2</td>
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<td>2.3 ± 1.3</td>
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<td>(N = 63)</td>
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<td>50 (60)</td>
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<td>3–5</td>
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<td>30 (36)</td>
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<tr>
<td>5</td>
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<td>3 (4)</td>
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<tr>
<td>Nocturnal defection</td>
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<tr>
<td>24 (29)</td>
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<tr>
<td>Fecal urgency</td>
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<td>16 (19)</td>
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<tr>
<td>Pad wearing</td>
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<tr>
<td>38 (46)</td>
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<tr>
<td>Intestinal transit regulators</td>
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<tr>
<td>22 (26.5)</td>
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<tr>
<td>Feces-flatus discrimination</td>
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<td>21 (25.3)</td>
</tr>
<tr>
<td>Stool fragmentation</td>
</tr>
<tr>
<td>40 (41)</td>
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<tr>
<td>Low fiber diet</td>
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<tr>
<td>30 (36)</td>
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Values inside parentheses indicate percentages.

<table>
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<tr>
<th>TABLE 4. Factors Influencing Functional Results</th>
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<tbody>
<tr>
<td>Continent</td>
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<tr>
<td>Sex</td>
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<td>Male</td>
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<td>Female</td>
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<tr>
<td>Preoperative radiotherapy</td>
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<tr>
<td>No</td>
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<tr>
<td>Yes</td>
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<tr>
<td>Dose of preoperative radiotherapy</td>
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<tr>
<td>0 Gy</td>
</tr>
<tr>
<td>25 Gy</td>
</tr>
<tr>
<td>45 Gy</td>
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<tr>
<td>Level of internal sphincter resection</td>
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<tr>
<td>Upper third</td>
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<tr>
<td>Upper half</td>
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<tr>
<td>pT stage</td>
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<td>pT0–pT1–pT2</td>
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<td>pT3–pT4</td>
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<tr>
<td>Tumor stage</td>
</tr>
<tr>
<td>I–II</td>
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<td>III–IV</td>
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| TABLE 5. Factors Influencing Functional Outcome: Multivariate Analysis |
|-----------------------------|-----------------------------|-----------------------------|
| Age                         | 1.03 (0.98; 1.08)           | 0.20                        |
| Gender                      | 1.14 (0.37; 3.52)           | 0.82                        |
| Stage                       |                             |                             |
| 0-1-2                       | 1                           |                             |
| 3-4                         | 1.31 (0.44; 3.95)           | 0.63                        |
| Preop. radiotherapy         | 3.07 (1.05; 8.98)           | 0.04                        |

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Annals of Surgery • Volume 246, Number 6, December 2007
Results of Intersphincteric Resection


REFERENCES

Professor Neil Mortensen: This paper confirms that cancer outcomes are not compromised. It is honest about the effects of partial resection of the internal sphincter, which does have the cost or consequence of poor function in about 25% of patients.

I have 2 questions. Number one, in your conclusion you say “in selected patients” and I wonder if you could expand on that a little more? For example, the trend toward the increasing use of preoperative chemoradiotherapy will obviously have an effect on sphincter function. Female patients may have a previous obstetric injury. Are these patients selecting themselves because they desperately do not want a colostomy, or are you steering them in the best direction to help them understand how good or otherwise their function is going to be?

Number two, you have treated around 10 patients per year, latterly more patients, maybe 15 to 18 patients per year,
and that is in a referral center. Does this suggest that many unnecessary abdominoperineal excisions are being carried out in the rest of the rectal cancer population?

Professor E. Tiret: First, as to the selection of patients, there are 2 different problems. The first is the tumor itself. I think that this operation should only be undertaken for early tumors, T1 or T2, at least very distally, close to the sphincter. The tumor must spare the levator ani or external sphincter. It is technically possible to resect part of the levator ani and I know that Japanese surgeons do this, but I think that the functional outcome will never be very good.

We did not do any preoperative manometry, which is probably not very helpful for these very low tumors. We selected patients on clinical inquiry. This operation is contraindicated if there is any evidence of incontinence preoperatively, that is, before the tumor became symptomatic. If the patient is fully continent, then we suggest this operation, telling the patient that there may be some degree of incontinence and that it is very difficult to predict who will be incontinent and who will be fully continent after surgery.

Your second question is about the number of abdominoperineal excisions. I said that, in the last years, we have done probably 20 per year. It is still a low percentage of patients who are operated on during the same time as rectal cancer as we treat more than 150 rectal cancer patients each year. And we continue to do many abdominoperineal excisions because, as you said, we are a referral center. Many patients with very low rectal cancer come to us seeking sphincter preservation, which turns out not to be feasible. We still continue to do more abdominoperineal excisions than intersphincteric resections.

Professor Neuhaus: I enjoyed the paper but I missed the number of positive lymph nodes. One option for early small tumors at this position is transanal full thickness excision of the wall. You have about 20% T0 and T1-patients and 40% T2-patients. In many centers, even higher tumors are only locally excised with full thickness of the wall with transanal endoscopic operative devices. Is there a role for these local excisions in your clinic? Where do you differentiate between low resection and local excision, also using endoultrasound or MRI for preoperative staging?

Professor Tiret: We had 7 patients who were pT0. That means that they are not T1 or T0 before the operation but T0 after preoperative chemoradiotherapy. Concerning the discussion about local excision, I totally agree with you that some very early superficial tumors can be treated by local excision. This requires good endosonography and we only do this operation for very selective patients with a T1 and, probably, sm1. Now it is possible to see, using a high-frequency probe for endorectal sonography, which part of the submucosa is invaded by the tumor. We know that local excision is a very good operation for T1 with mucosal invasion or T1 sm1, which means invasion of the proximal part of the submucosa. However, if the tumor has reached the distal part of the submucosa (sm3), or invades the muscular layer, it is not a good indication for local excision.

Professor O'Connell: I just have 1 question that goes back to your first publication of your early experience in which your anastomotic leak rate was somewhat higher. What have you learned over the years that has reduced your anastomotic leak rate?

Professor Tiret: I think it is just a different number of patients as we have not changed our surgical technique over time. I am sorry, I wish I learned something to decrease the leak rate but, unfortunately, this is not the case.
Pancreatic Head Resection With Segmental Duodenectomy

Safety and Long-Term Results

Akimasa Nakao, MD, PhD,* and Laureano Fernández-Cruz, MD, PhD, FRCS†

Objective: To evaluate the usefulness and long-term results with pancreatic head resection with segmental duodenectomy (PHRSD; Nakao’s technique) in patients with branch-duct type intraductal papillary mucinous neoplasms (IPMNs). A prospective study from Nagoya (Japan) and Barcelona (Spain).

Summary Background Data: Surgery should be the first choice of treatment of IPMNs. An aggressive surgery (eg, pancreatoduodenectomy) should be questioned in patients with an indolent disease or with noninvasive tumors. Recently, organ-preserving pancreatic resections for benign and noninvasive IPMN located in the head of the pancreas have been described. We have PHRSD in which the pancreatic head can be completely resected and the major portion of the duodenum can be preserved by this procedure. There have been only 4 reports concerning PHRSD with <8 patients (each one) in the English literature.

Methods: Thirty-five patients underwent PHRSD (20 men, 15 women), mean age 65.1 ± 9.0 (range, 55–75). Mean maximal diameter of the cystic lesion was 26.4 ± 5.3 mm (range, 20–33 mm) and mean diameter of the main pancreatic duct was 3.3 ± 0.5 mm (range, 3.0–4.0 mm). Alimentary tract reconstruction was performed in 20 patients by pancreato gastro stomy, duodenoduodenostomy, and choledochoduodenostomy (type A) and 15 patients by pancreatico jejunostomy, duodenoduodenostomy and choledochojejunostomy (Roux-en-Y; type B). Surgical parameters, postoperative complications, endocrine function, exocrine function, and long-term outcomes were evaluated. To compare the perioperative factors, a matched-pairs analysis between PHRSD patients and patients with pylorus preserving pancreaticoduodenectomy (PPPD) was performed. In the latter group were included 32 patients with branch-duct type of IPMN operated during the same time period that patients with PHRSD. The mean follow-up period was 48.8 months.

Results: Mean operative time after PHRSD was 365 ± 50 and mean surgical blood loss was 615 ± 251 mL. There was no mortality. Pancreatic fistula occurred in 10% and 13% with types (alimentary tract reconstruction) A and B, respectively. Noninvasive IPMN was found in 31 patients and invasive IPMN in 4 patients (11.4%). In the matched-pairs analysis between PHRSD and PPPD, the 2 procedures were comparable in regard to operation time and intraoperative blood loss. The overall incidence of pancreatic fistula was higher after PPPD than after PHRSD; the difference was not statistically significant. When fistulas occurred after PHRSD they were grade A (biochemical). In contrast, pancreatic fistulas after PPPD were grade A in 78% of cases and grade B in 22% (clinically relevant fistula). The incidence of delayed gastric emptying was significantly higher in the PPPD group compared with the PHRSD group (P < 0.01). Endocrine pancreatic function, measured by fasting blood glucose levels and HbA1, levels was unchanged in 94.28% of patients, in the PHRSD group, and in 87.87% in the PPPD group. Body weight was unchanged in 80% after PHRSD and in 59% after PPPD. Postoperative enzyme substitution was needed in 20% of patients after PHRSD and in 40% patients after PPPD. The 5-year survival rate was 100% in patients with benign IPMN and 42% in patients with invasive IPMN.

Conclusion: PHRSD is a safe and reasonable technique appropriate for selected patients with branch-duct IPMN. The major advantages of PHRSD are promising long-term results in terms of pancreatic function (exocrine and endocrine) with important consequences in elderly patients. Long-term outcome was satisfactory without tumor recurrence in noninvasive carcinoma. PHRSD should therefore be considered as an adequate operation as an organ-preserving pancreatic resection for branch-duct type of IPMN located at the head of the pancreas.

nanty involving the side branch of the ductal system (branch-duct type), because they have different tumor biologic behavior.\textsuperscript{10–13} Branch-duct type IPMN is less often associated with invasive carcinoma than main type IPMN. However, the difference in the prognosis of the main-duct type and the branch-duct type is still a controversial issue.\textsuperscript{2,3,7}

Among the surgical techniques performed, pancreati
coduodenectomy, distal or total pancreatectomy, are reserved for patients with invasive adenocarcinoma. However, this aggressive surgery should be questioned in patients with an indolent disease or with noninvasive tumors. Organ-preserving pancreatic resections are reasonable surgical options.\textsuperscript{14–20} The major problems with these techniques, such as duodenum-preserving pancreatic head resection (DPPHR) and partial resection of the pancreatic head, are the uncertainty to complete extirpation of IPMN, because IPMN tends to spread into the main or branch pancreatic ducts, and the potential postoperative complications associated to ischemia of the common bile duct and the duodenum.\textsuperscript{20,21} To avoid these problems, pancreatic head resection with segmental duode
cotomy (PHRSD) has been described as an organ-preserving pancreatic resection.\textsuperscript{22,23} In this operation, the pancreatic head can be completely resected without causing ischemia of the common bile duct and the duodenum, and the major portion of the duodenum can be preserved by this procedure.

There have been only 4 reports performing PHRSD for IPMN located at the head of the pancreas, in the English literature, including no more than 8 patients in each publication.\textsuperscript{23–26} The aim of this study is to report the safety and long-term outcome of PHRSD from 2 tertiary referral centers and to discuss implications for operative technique and patient selection.

\section*{PATIENTS AND METHODS}
\subsection*{Patient Characteristics}

Data for patients undergoing PHRSD between March 1996 and March 2006 were prospectively entered into a standardized electronic database in the Department of Surgery of Nagoya University Hospital, Japan and in the Department of Surgery of Hospital Clinic, Barcelona, Spain and subsequently analyzed. All patients had branch-duct type of IPMN <30 mm in diameter located at the head of the pancreas. The indication for surgery was a symptomatic lesion in 80% of patients, mainly abdominal pain and episodes of mild pancreatitis.

Preoperative staging included computed tomography and cholangio-magnetic-resonance imaging, with most patients undergoing additional evaluation with endoscopic ultrasound and puncture fine needle aspiration for histologic studies.

The patients who underwent PHRSD consisted of 35 patients (22 men and 13 women), mean age 65.1 ± 9.0 (range, 55–75). Mean maximal diameter of the cystic lesion was 26.4 ± 5.3 mm (range, 20–33 years) and mean diameter of the main pancreatic duct was 3.3 ± 0.5 mm (range, 3.0–4.0).

\subsection*{Surgical Procedure}

Laparotomy was done by upper midline skin incision. The gastrocolic and duodenocolic ligament is divided with preservation of right gastroepiploic artery and vein to explore the front of the pancreas. The right gastroepiploic vein is ligated and divided at the root. The anterior-superior pancreaticoduodenal artery, the posterior-superior pancreaticoduodenal artery, and few other branches from gastroduodenal artery (GDA) toward the pancreas were ligated and divided. By conserving the right gastroepiploic artery and GDA, 5 to 7 cm of the first portion of the duodenum is preserved with good arterial circulation. The pancreas is divided on the line of the portal vein. The extrapancreatic nerve plexus between the uncinate process and the superior mesenteric artery is preserved, so the inferior pancreaticoduodenal artery is preserved. The anterior-inferior pancreaticoduodenal artery (AIPDA) is preserved and the posterior-inferior pancreaticoduodenal artery is ligated and divided. The AIPDA is ligated and divided near the major papilla (Fig. 1). The common bile duct is divided at the upper border of the pancreas. Two to 3 cm of ischemic area of the duodenum including major and minor papilla is observed. The oral side of the duodenum is divided at 5 to 7 cm from the pyloric ring. The anal side of duodenum is divided at the point of AIPDA ligation. Thus, PHRSD with preservation of GDA is completed. The length of the resected duodenum ranged from 3 to 5 cm (Fig. 2).
The reconstruction of the alimentary tract was performed according to the Nakao’s original technique (type A) in 20 patients: pancreaticogastrostomy (temporary pancreatic stent into the main pancreatic duct of the remnant pancreas and drained externally), end-to-end duodenoduodenostomy, and end-to-side choledochoduodenostomy (temporary transhepatic biliary stenting) (Fig. 3). In 15 patients, reconstruction (type B) was accomplished with a 40 to 60 cm retrocolic Roux-en-Y limb of jejunum. And end-to-side pancreaticojunostomy was constructed using duct to mucosa anastomosis; a pancreatic stent was inserted into the main pancreatic duct of the remnant pancreas and drained externally. Reconstruction was completed by end-to-side choledochojunostomy (temporary T-tube of Kher) and finally, end-to-side Roux-en-Y enterenterostomy 20 to 25 cm distal to the ligament of Treitz (Fig. 4). The indication for cholecystectomy was based on individual decision of the surgeon or by the presence of gallbladder stones.

CLINICAL DATA ANALYSIS

Data on operative, intraoperative, and postoperative care were prospectively collected. Preoperative parameters include patient demographics (age, gender); intraoperative parameters include total operative time, blood loss, and blood transfusion. Postoperative events were recorded according to the following definitions. Delayed gastric emptying: failure to resume oral liquid intake by postoperative day 10, and/or emesis >500 mL on or after postoperative day 5, and/or continued nasogastric drainage >500 mL on or after postoperative day 5. Biliary leak: bilious drainage from intraoperatively placed drains. Gastrointestinal bleed: guaiac-positive hematemesis, hematoccexia, or melena or the sudden appearance of frank blood either on nasogastric lavage or per rectum. Length of stay: days from the initial operation to hospital discharge. Pancreatic fistula, according to the International Study Group on pancreatic fistula, was designed as any measurable drainage from an operatively placed drain on
or after postoperative day 3, with an amylase content greater than 3 times the upper limit of normal serum amylase level. Those patients with fistula were then classified into 3 grades of severity according to International Study Group on pancreatic fistula clinical criteria.27

To compare the perioperative factors, a matched-pairs analysis between PHRSD patients and patients with pylorus preserving pancreaticoduodenectomy (PPPD) was performed. In the latter group were included 32 patients with branch-duct type of IPMN operated during the same time period that patients with PHRSD, with some features suggesting malignancy such as jaundice, and cystic tumors greater than 35 mm in diameter.

The postoperative long-term outcomes, including pancreatic endocrine and exocrine function, and recurrence, were also evaluated. The endocrine function was measured by fasting glucose and serum hemoglobin (HbA1) levels. The exocrine function was evaluated by changes in the body weight of the patients and the need of postoperative enzyme substitution.

The median follow-up period was 37.5 months for PHRSD patients and 76.2 months for PPPD patients. Results were presented as mean ± standard deviation. The surgical complication rates were compared with respect to the surgical procedure (PHRSD vs. PPPD) and between the 2 types of surgical reconstruction after PHRSD (type A vs. type B), using the Fisher exact test. Two-sided P values were always computed, and an effect was considered statistically significant at P <0.05.

RESULTS

Perioperative Data in Patients After PHRSD

All tumors were resected with clear surgical margins, as shown by intraoperative frozen sections and confirmed by definitive histopathological examinations.

The mean operation time after PHRSD was 365 ± 50 (range, 120–490 minutes). The mean intraoperative blood loss was 615 ± 251 (range, 200–1500 mL). One patient received blood transfusions (2 units). The mean intensive care stay was 1 day.

Four patients (11.4%) developed pancreatic fistula with subsequent spontaneous resolution within 3 weeks. All fistula meet criteria for grade A fistula (transient, asymptomatic fistula, evident only by elevated drain amylase levels). Five patients (14%) developed delayed gastric emptying. Medical complications were observed in 2 patients, including pleural effusions in 1 and pneumonia in 1 patient. Twenty-four patients (62.8%) had uneventful postoperative course.

Twenty patients with PHRSD and pancreaticogastrostomy reconstruction were compared with 15 patients with PHRDS and pancreaticojejunostomy anastomosis. There was no difference in perioperative factors between the 2 groups. The postoperative mean hospital stay was 28.3 ± 14.2 days after PHRDS with type A alimentary tract reconstruction (patients operated on at the Nagoya University). Interestingly, for only 15% of these patients the start of diet began after 21 postoperative days (delayed gastric emptying). However, the length of hospital stay was 12 ± 4.0 days after PHRSD with type B alimentary tract reconstruction (patients operated on at the Barcelona, Hospital Clinic). There were no differences in the postoperative complication rates between the 2 Institutions (Table 1). Therefore, differences in medical culture may explain the disparity of in-hospital stay in this combined experience.

Matched-Pairs Analysis and Postoperative Long-Term Follow-Up

In the matched-pairs analysis 35 patients with PHRSD and 32 patients with PPPD were included. The groups were well matched with regard to age and gender. The 2 procedures were comparable in regard to operation time and intraoperative blood loss (Table 2). The overall incidence of pancreatic fistula was higher after PPPD (22%) than after PHRSD (11%); the difference was not statistically significant. In the PPPD group, 60% had pancreaticogastrostomy technique and 40% had pancreaticojejunostomy technique. When fistulas occurred after PHRSD they were grade A (biochemical). In contrast, pancreatic fistulas after PPPD were grade A in 78% of cases and grade B in 22% (clinically relevant fistula). The incidence of delayed gastric emptying was significantly higher in the PPPD (31%) compared with the PHRSD group (14%; P < 0.01).

Endocrine pancreatic function measured by fasting blood glucose levels and HbA1c levels was unchanged in 94.28% of patients in the PHRSD group and in 87.87% of patients in the PPPD group.

Body weight was unchanged in 80% of patients after PHRSD and in 59% of patients after pylorus-preserving (pp)-Whipple. Postoperative enzyme substitution was needed in 20% of patients after PHRSD and in 41% patients after PPPD (P < 0.05; Table 2).

Histopathology and Tumor Recurrence

Definitive histology of the resected lesions after PHRSD revealed 27 IPMN adenoma, 4 had carcinoma in situ, 15% of these patients the start of diet began after 21 postoperative days (delayed gastric emptying). However, the length of hospital stay was 12 ± 4.0 days after PHRSD with type B alimentary tract reconstruction (patients operated on at the Barcelona, Hospital Clinic). There were no differences in the postoperative complication rates between the 2 Institutions (Table 1). Therefore, differences in medical culture may explain the disparity of in-hospital stay in this combined experience.

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Histopathology and Tumor Recurrence

Definitive histology of the resected lesions after PHRSD revealed 27 IPMN adenoma, 4 had carcinoma in situ,
TABLE 2. Matched Pairs Analysis Comparing Patients With PHRSD and Patients With pp-Whipple

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>PHRSD (N = 35)</th>
<th>pp-Whipple (N = 32)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>65.1 ± 9.0</td>
<td>61.7 ± 8.8</td>
<td>NS</td>
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<tr>
<td>Female</td>
<td>15</td>
<td>14</td>
<td>NS</td>
</tr>
<tr>
<td>Male</td>
<td>20</td>
<td>18</td>
<td>NS</td>
</tr>
<tr>
<td>Perioperative results</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Operating time (Min)</td>
<td>367 ± 69</td>
<td>375 ± 89</td>
<td>NS</td>
</tr>
<tr>
<td>Surgical blood loss (mL)</td>
<td>667 ± 185</td>
<td>825 ± 453</td>
<td>NS</td>
</tr>
<tr>
<td>Pancreatic fistula</td>
<td>4 (11%)</td>
<td>7 (22%)</td>
<td>NS</td>
</tr>
<tr>
<td>Biliary leakage</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Bleeding</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Delayed gastric emptying</td>
<td>5 (14%)</td>
<td>10 (31%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Mortality</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Postoperative diabetes mellitus</td>
<td>2 (6%)</td>
<td>3 (9%)</td>
<td>NS</td>
</tr>
<tr>
<td>Follow-up weight:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unchanged</td>
<td>28 (80%)</td>
<td>19 (59%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Increased (3 kg up)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Loss (3 kg down)</td>
<td>7 (20%)</td>
<td>13 (41%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Postoperative enzyme substitution</td>
<td>7 (20%)</td>
<td>13 (41%)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

TABLE 3. Histopathology and Follow-Up After PHRSD and pp-Whipple

<table>
<thead>
<tr>
<th>Follow-up periods (mo)</th>
<th>PHRSD (N = 35)</th>
<th>pp-Whipple (N = 32)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>42.8 ± 27.7</td>
<td>76.2 ± 48.9</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>37.5</td>
<td>73.4</td>
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</tr>
<tr>
<td>Adenoma</td>
<td>27</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Carcinoma in situ</td>
<td>4</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Invasive carcinoma</td>
<td>4 (11%)</td>
<td>7 (22%)</td>
<td></td>
</tr>
<tr>
<td>Clinical follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alive</td>
<td>33</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Dead</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Recurrence</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

and 4 had invasive carcinoma. Two patients with invasive cancer died 3 and 5 years after surgery with peritoneal dissemination. In the PPPD group, 6 patients had carcinoma in situ and 7 had invasive cancer. In this group, 4 patients died 3, 4, 6, and 7 years after surgery with peritoneal dissemination (2 patients) and liver metastasis (2 patients) (Table 3).

DISCUSSION

IPMN is a slow growing and low malignancy tumor. Complete removal of the tumor results in a good prognosis. However, when invasive carcinoma is found the prognosis is significantly worse. It is now known that IPMN can arise in the main duct or in the side branches ducts. The latter is less often associated with invasive carcinoma than main-duct type IPMN. However, the difference in the prognosis of the main-duct type and the branch-duct type is still a controversial issue. In the series, Sohn et al and D’Angelica et al reported that there was no significant difference in survival between the main-duct type and the branch-duct type. Therefore, the diagnosis of invasion or noninvasion is very crucial in this disease. A number of retrospective studies have been performed to identify the clinical pathologic features that can differentiate malignant IPMN from benign IPMN. The following features suggest malignant IPMN: jaundice, worsening or new onset of diabetes mellitus, main-duct type tumor, tumor size >30 mm, mural nodule size >5 mm, and carcinoembryonic antigen levels >110 mg/mL in pure pancreatic juice.

Several authors reported that the branch-duct type of IPMN without mural nodule was always benign; the necessity of resection in all these patients has been questioned, and conservative management with observation alone has been described. However, the concern for actual or potential malignancy in IPMN is real, and the recommendation to proceed with resection may be justified in most suitable candidates. In the present series, invasive carcinoma was found in 11% of patients with branch-duct type IPMN <30 mm in diameter. In recent series, the frequency of invasive carcinoma in branch-duct type IPMN varies from low figures 0% and 6% to high figures 30% to 46%. In all reports, tumor size >30 mm is a strong predictive factor of malignant IPMN.

Surgical resection remains the option that gives the best chance of cure. For invasive IPMN, extended pancreatic resection including pancreaticoduodenectomy is required, because metastasis to the regional lymph nodes or invasion to the surrounding organs frequently occurs in these patients. Conversely, organ-preserving pancreatic resection is advocated for patients with benign IPMN. Various modifications of organ-preserving pancreatic resections for IPMN have been reported, DPPHR resection (Beger’s technique), DPPHR with complete resection of the pancreatic head, inferior head resection of the pancreas, and ventral pancreatectomy. According to Murakami et al, there are major problems with these procedures. It is very difficult to ensure complete extirpation of IPMN with partial resection of the pancreatic head, because IPMN tends to spread into the main or branch pancreatic ducts. One patient with IPMN who died of recurrent disease 18 months after inferior head resection was reported. Postoperative ischemic necrosis or perforation of the common bile duct and the duodenum occasionally occur with DPPHR with preservation of the common bile duct. DPPHR with complete resection of the pancreatic head makes technically impossible to preserve the branches of the posterior-superior pancreaticoduodenal artery, which runs through the pancreatic parenchyma between the common bile duct and the duodenum and toward the major papilla. In addition, if DPPHR with resection of the common bile duct is performed for complete resection of the pancreatic head, ischemia of the major papilla may also occur. DPPHR with incomplete resection of pancreatic head and preservation of the intrapancreatic main bile duct (Beger’s operation) was performed in 13 patients, with IPMN.
A high morbidity was observed in this series, anastomosis pancreatic leakage (15%), bile duct perforation (8%), intra-peritoneal bleeding (15%), delayed gastric emptying (15%), and a mortality rate of 15%. This high morbidity differs from the low morbidity of DPPHR in patients with chronic pancreatitis.36–38

PPPD is the most commonly performed organ-preserving procedure for diseases of the pancreatic head region. Pancreaticoduodenectomy can be performed in experienced centers with mortality rate below 0.5%39 and 3%,40 however, this procedure represents surgical overkill for benign or low-grade malignant IPMN. In the present series, there was no mortality due to either PHRSD or PPPD.

After pancreaticoduodenectomy, the incidence of diabetes mellitus varies between 15% and 40%41. In our current series, endocrine pancreatic function was unchanged in 94% and 88% after PHRSD and pp-Whipple, respectively. In the present series, postoperative enzyme substitution was needed in 20% of PHRSD patients and 41% of PPPD patients. Enzyme therapy was given to patients with steatorrhea or weight loss. These results suggest that endocrine and exocrine pancreatic function is better preserved after PHRSD than after PPPD.

Nakao et al22 was the first to describe PHRSD in 1994. In 1998,23 he reported 14 patients with PHRSD including mucin-producing cystic tumors (9 cases), annular pancreas (1 case), anomalous arrangement of the pancreatico-biliary ductal system (1 case), carcinoma of the duodenum (1 case), carcinoma of the Ampulla of Vater (1 case), and cancer of the common bile duct (1 case). More recently, PHRSD was performed in patients with low-grade malignant diseases of the pancreatic head region including IPMN. In the Isaji and Kawarada24 series, 6 benign IPMN and 2 invasive IPMN were reported, with a follow-up of 36 and 22 months, respectively, without tumor recurrence. Alimentary tract reconstruction was performed in 4 patients with anastomosis of the pancreatic duct to the duodenum and in 4 patients with pancreaticojejunostomy. Postoperative complications occurred in 2 patients, 1 developed acute pancreatitis and 1 developed methicillin-resistant *Staphylococcus aureus* enteritis. Murakami et al26 reported 8 patients with branch-duct type IPMN. In all cases a pancreaticogastrostomy, duodenoduodenostomy, and choledochoduodenostomy were performed. Complications after PHRSD occurred in 4 patients, 1 with pancreatic leak, 1 with choledochoduodenal anastomosis stenosis, and 2 with delayed gastric emptying. The final pathologic diagnosis was adenoma in 7 patients and carcinoma in situ in 1 patient. Postoperative pancreatic endocrine and exocrine functions were satisfactory. All patients were alive without recurrent disease at a median follow-up of 30 months.

In this current study, PHRSD was performed with 2 different alimentary tract reconstructions, pancreaticogastrostomy in 1 group and pancreaticojejunostomy in another group. Despite the anastomosis was performed with a soft pancreas, the data of our present study indicate that both techniques are safe with morbidity rates comparable.

The major advantages of PHRSD are as follows: (1) To complete resection of the pancreatic head, safely, without ischemia of the common bile duct and duodenum. (2) Preservation of endocrine pancreatic function probably by maintaining the duodenal passage of foods resulting in a physiologic entero-insular axis. (3) Exocrine pancreatic function was altered little in some patients, requiring postoperative enzyme substitution. Body weight was unchanged in the majority of patients.

Because of limited oncologic radicality, PHRSD is only an adequate option in patients with benign and noninvasive IPMN. The lesion and resection margins should therefore be examined by frozen section during the operation. The resection should be extended if the ductal margin shows malignant invasive disease. In these circumstances, the lymph node dissection should be completed including the areas of hepatic hilum, celiac trunk, and along the superior mesenteric artery.

**CONCLUSIONS**

PHRSD is a safe and reasonable technique appropriate for selected patients with branch-duct IPMN. The major advantages of PHRSD are promising long-term results in terms of pancreatic function (exocrine and endocrine) with important consequences in elderly patients. Long-term outcome was satisfactory without tumor recurrence in noninvasive carcinoma. PHRSD should therefore be considered as an adequate operation as an organ-preserving pancreatic resection for branch-duct type of IPMN located at the head of the pancreas.

**REFERENCES**


11. Matsumoto T, Aramaki M, Yada K, et al. Optimal management of the...


**Discussions**

**PROFESSOR H. BEGER:** Thank you for an elegant presentation with convincing data regarding a new indication for DPPHR including a segmental resection of the duodenum. Your data are in accordance with recently published data regarding application of this limited surgical procedure for primary benign lesions of the pancreatic head as a standard procedure.

To achieve complete removal of the lesion, it is necessary to perform total exirpation of the head. You have done this in a large series of patients with side branch IPMN lesions. However, for this specific type of IPMN lesion, 30% multifocality has been reported. To choose the appropriate surgical procedure, the surgeon needs to be able to discriminate benign from malignant lesion. During the surgical procedure, frozen section is mandatory to be complete in terms of having all the IPMN tissue removed or to switch to a pp-Whipple procedure in cases of an invasive carcinoma. How did you manage the multifocality in side-branch IPMN lesions and completeness of the resection? You have applied this limited surgical procedure in 4 patients, who ultimately had an invasive ductal pancreatic cancer. However, DPPHR in advanced pancreatic cancer is an inadequate procedure. As a consequence of this failure, using duodenum-preserving resection, 2 patients developed local recurrence of the cancer in a short postoperative period. Recurrence may even have developed in patients after incomplete resection of benign IPMN lesions as we experienced in 2 of 4 patients, in which we applied a subtotal duodenum-preserving resection of the pancreatic head. For recurrent benign lesions after subtotal head resection, a pp-Whipple was applied. From this institutional experience, we concluded that, in all patients with cystic neoplastic head lesions, we needed to perform a total...
DPPHR including a segment of the duodenum, to ensure completeness of removal of the neoplastic lesion.

I am wondering about your techniques of reconstruction. In the Barcelona patients for biliary reconstruction you used a second large single jejunal loop. Did you observe using 2 excluded jejunal loops, signs of malabsorption? Please comment on this. We are using 1 excluded jejunal loop similar to the Nakao-technique, performing a pancreaticojunostomy and implantation of the common bile duct in the preserved duodenum.

PROFESSOR L. FERNÁNDEZ-CRUZ: Concerning your first question, I think these operations should be performed in patients with benign lesions and, in the group of patients with premalignancy lesions, we know that they probably would not be malignant. I say probably, because certainty in discriminating between benign and malignancy is very difficult in this group of patients. What we do in Barcelona is to undertake endoscopic ultrasonography and aspiration cytology on all of our patients, and by doing so we can discriminate benign from malignant lesions in a high number of patients. In Japan, they use endoscopic retrograde cholangiopancreatography, aspirate the pancreatic juice and they measure carcinoembryonic antigen levels. When they see that it is above 110, the patients probably do have malignant tumors and, for them, the endoscopic retrograde cholangiopancreatography helps in discriminating between benignity and malignancy. In most of our patients, we were successful in dealing with benign lesions. However, 11% were malignant. But, let me just remind you that, in Edinburgh in the last International HPB meeting, I presented our experience in dealing with benign lesions. However, 11% were malignant. Concerning your last comment on the myth in the patients with preserving pancreatic head resection, I think Professor Beger and Marcus Büchler did a beautiful study in patients with total gastrectomy for gastric cancer and they investigated whether the different types of reconstruction could influence the possible outcome in terms of endocrine pancreatic function. I think that by preserving the duodenum, there is a real benefit. It was published and demonstrated by these 2 authors and I do not think it is a myth. I think it is supported by our results. As for exocrine pancreatic function, unfortunately, we did not measure fecal elastase. We did so in some patients but this was not presented today. I think that the only way to know whether the exocrine pancreatic function is preserved is by measuring fecal elastase. Nevertheless, patients in the group of pancreatic resections with duodenectomy needed less enzyme substitution compared with pylorus preserving Whipple. This is, therefore, a beneficial effect of the operation.

MR C. RUSSELL: I enjoyed this article greatly and it was a reminder of work that my group undertook on the vascular supply of the duodenum. The reason why duodenal preservation is feasible is that the submucosal anastomotic networks are the same as in the stomach in contrast to the segmented blood supply of the small intestine. Perfusion studies show that there is a submucosal anastomosis between one end of the duodenum and the other, thus perfuse injected distally will reflux up to the pylorus. We found that preservation of the duodenum was safe, provided that a reasonable length of the inferior pancreaticoduodenal artery was preserved. So, my first question is, why did you resect the small segment because, if you are dealing with benign disease, you can divide it at the ampulla without damaging the duodenum.

The second point is that my disappointment with duodenal preservation was the failure to show a clinical advantage. Our 9 patients with duodenal-preserving pancreaticojejunostomy were no different from matched controls that had a pylorus preserving pancreaticojejunostomy regarding weight and quality of life. Indeed, your long lengths of stay show that some of these patients do take quite a long time to recover possibly because the anastomosis that you do functions al-
most as another pylorus. I wondered if you did emptying studies during the postoperative period to show why they took a mean of 48 days to recover.

Professor L. Fernandez-Cruz: Concerning the technical aspects of the operation and your comments referring to your work in this area, I recall that the great majority of your patients were chronic pancreatitis patients, and generally, they are a different type of patient. The great majority have impairment of both exocrine and endocrine pancreatic function. That is why you cannot expect to see good results in the endocrine and exocrine pancreatic function because you start with impairment in these 2 important functions of the pancreas. I do not think your group of patients with chronic pancreatitis is comparable. Our group of patients had normal pancreatic function with no signs of chronic pancreatitis.

As to your second question, I think it is necessary to preserve the arteries that were described. Once we removed the head of the pancreas with the second part of the duodenum, when we do the vascular preservation and the ligation of the arteries that were discarded, all patients experienced a change in the color of the duodenum. The second part of the duodenum became black in most of them. That is why I think the preservation of these arteries is crucial and we should be very meticulous in their preservation. I think, in this area, the Santorini and the Wirsung duct go to this area and I think should be resected with the head of the pancreas.

Professor A. Kingsnorth: You are trying to sell the operation on the basis that you get poor endocrine and exocrine function after the standard Whipple but this is improved with your operation. You did not tell us, though, in the matched pairs group, which had pancreaticogastrostomy and which had pancreaticojejunostomy because we now know that the exocrine function after pancreaticojejunostomy is much better. Now, the Japanese have been performing pancreaticogastrostomy. Did you match pair for that in your Whipples operations or did they all receive the Spanish pancreaticogastrostomy?

Professor L. Fernandez-Cruz: No. In the pylorus-preserving group, the patients operated on in Nagoya had a pancreaticogastrostomy and, in Barcelona, a pancreaticojejunostomy.

Professor A. Kingsnorth: So you controlled for the type of pancreatic reconstruction?

Professor L. Fernandez-Cruz: Yes.
Objective: To assess the reliability of 18-fluorodeoxyglucose positron emission tomography (18-FDG PET) in distinguishing benign from malignant intraductal papillary mucinous neoplasms (IPMNs) of the pancreas and its contribution to surgical decision making.

Summary Background Data: Pancreatic IPMNs are increasingly recognized, often as incidental findings, especially in people over age 70 and 80. Computed tomography (CT) and magnetic resonance (MR) are unreliable in discriminating a benign from a malignant neoplasm. 18-FDG PET as imaging procedure based on the increased glucose uptake by tumor cells has been suggested for diagnosis and staging of pancreatic cancer.

Methods: From January 1998 to December 2005, 64 patients with suspected IPMNs were prospectively investigated with 18-FDG PET in addition to conventional imaging techniques [helical-CT in all and MR and magnetic resonance cholangiopancreatography (MRCP) in 60]. 18-FDG PET was analyzed visually and semiquantitatively using the standard uptake value (SUV). The validation of the diagnosis was made by a surgical procedure (n = 44), a percutaneous biopsy (n = 2), main duct cytology (n = 1), or follow-up (n = 17). Mean and median follow-up times were 25 and 27.5 months, respectively (range, 12–90 months).

Results: Twenty-seven patients (42%) were asymptomatic. Forty-two patients underwent pancreatic resection, 2 palliative surgery, and 20 did not undergo surgery. An adenoma was diagnosed in 13 patients, a borderline tumor in 8, a carcinoma in situ in 5, and an invasive cancer in 21; in 17 patients a tumor sampling was not performed and therefore the histology remained undetermined. Positive criteria of increased uptake on 18-FDG PET was absent in 13 of 13 adenomas and 7 of 8 borderline IPMNs, but was present in 4 of 5 carcinoma in situ (80%) and in 20 of 21 invasive cancers (95%). Conventional imaging technique was strongly suggestive of malignancy in 2 of 5 carcinomas in situ and in 13 of 21 invasive carcinomas (62%). Furthermore, conventional imaging had findings that would be considered falsely positive in 1 of 13 adenomas (8%) and in 3 of 8 borderline neoplasms (37.5%). Therefore, positive 18-FDG PET influenced surgical decision making in 10 patients with malignant IPMN. Furthermore, negative findings on 18-FDG PET prompted us to use a more limited resection in 15 patients, and offered a follow-up strategy in 18 patients (3 positive at CT scan) for the future development of a malignancy.

Conclusions: 18-FDG PET is more accurate than conventional imaging techniques (CT and MR) in distinguishing benign from malignant (invasive and noninvasive) IPMNs. 18-FDG PET seems to be much better than conventional imaging techniques in selecting IPMNs patients, especially when old and asymptomatic, for surgical treatment or follow-up.

preoperative correct prediction of malignancy is important for establishing prognosis and for surgical decision-making. Jaundice and diabetes are associated with malignant tumors, but their accuracy as clinical predictors of malignancy is low.6 The reported radiologic features useful for the identification of malignant lesions are a dilated MPD ≥6 to 10 mm, a diameter greater than 3 to 4 cm, the presence of nodules and/or irregular septa, and the thickness of the wall of the cyst.5,7–9 However, the distinction between benign and malignant neoplasms is still difficult,10–12 even with endoscopic ultrasonography (EUS).13

Positron emission tomography with F-18-fluorodeoxyglucose (18-FDG PET) has an expanding role in the diagnosis and staging of several tumors14 including pancreatic adenocarcinoma.15,16 We previously reported that 18-FDG PET was very accurate in discriminating between malignant and benign cystic tumors of the pancreas,17,18 a small subset of IPMNs included.

The purpose of this study was to evaluate the usefulness of 18-FDG PET in detecting malignancy among a large cohort of patients with IPMNs of the pancreas and its relevance on clinical management of these patients.

METHODS

From January 1998 to December 2005, 71 patients with suspected IPMN of the pancreas were observed in our Department at University of Padua. Among them, 64 patients underwent 18-FDG PET in addition to conventional imaging techniques, and were prospectively investigated, whereas for 7 patients PET scan was not available. All patients also underwent physical examination, medical history evaluation, blood tests and serum CA 19-9 tumor marker determination (RIA; Centocor Inc., Malverne, PA; serum reference <37 U/mL), and helical computer tomography scanning (CT; interval, 2.5 mm thick). The preoperative work-up also included magnetic resonance (MR) and magnetic resonance cholangiopancreatography (MRCP) with intravenous injection of secretin (n = 60); MR and MRCP was not performed in 4 patients: 1 for claustrophobia, 1 because performed 1 year before, and 2 because of clear pattern of malignancy on CT scan. Patient characteristics included age, sex, presence or absence of symptoms, and presence or absence of diabetes mellitus. Radiographic and cyst characteristics included the presence of septations, a solid component or mural nodulation, pancreatic duct dilation, cyst size, and the pathologic diagnosis for resected lesions. If multiple cystic lesions were present within the pancreas, the diameter of the largest lesion was recorded. Malignant IPMNs were defined as IPMNs with high-grade dysplasia (carcinoma in situ), or invasive carcinoma; benign IPMNs were considered those with adenoma or borderline features.7

18-FDG PET images were obtained using a dedicated tomograph (ECAT EXACT 47; Siemens, Erlangen, Germany) with a field of view of 16.2 cm. After an overnight fast, 444 MBq (12 mCi) of 18-FDG was injected intravenously into each patient. To avoid interferences caused by hyperglycemia, blood glucose levels were checked just before the procedure and were decreased to <120 mg/dL with insulin administration whenever needed. Two transmission scans of the abdomen, 15 minutes each, were obtained by 68 Ge/68 Ga rod sources before the administration of 18-FDG to obtain cross-sections for attenuation correction of the emission images. Then, 2 emission scans, 15 minutes each, were acquired starting 60 minutes after the administration of 18-FDG. The reconstruction was performed in a 128 × 128 matrix with Hanning filter 0.3 cutoff. Transaxial, coronal, and sagittal sections were obtained for visual analysis. To perform a quantitative analysis, the standardized uptake value (SUV) was calculated in the suspected neoplastic foci (SUV = tissue tracer concentration/injected dose/body weight). For the SUV analysis, a circular region of interest was placed over the area of maximal focal 18-FDG uptake, and the mean radioactivity values were obtained. A focal uptake with an SUV of 2.5 or greater was considered positive according to our previous experience and literature reports.17–19 The reporting of each of the imaging modalities was reported blindly of the other results.

A validation of the diagnosis was based on the pathologic findings of a resected specimen biopsy examination, or follow-up. Follow-up evaluation included clinical examination, laboratory tests, CA 19-9 serum levels, and CT and/or MR and MRCP every 6 months. PET was performed at least 12 months after the first observation or in the case of clinical suspicion, tumor marker increase, or inconclusive results of conventional imaging techniques.

Sensitivity, specificity, positive (PPV) and negative predictive value (NPV), and accuracy of 18-FDG PET and CT/MR and MRCP in differentiating malignant from benign lesions were evaluated, according to the following formulas: sensitivity = TP/TP + FN; specificity = TN/TN + FP; PPV = TP/TP + FP; NPV = TN/TN + FN; accuracy = TP + TN/TP + TN + FP + FN, in which TP indicates true positive; TN, true negative; FP, false positive; and FN, false negative. Our policy in the management of patients with IPMNs was to perform resection, whenever possible, in all the symptomatic or PET positive lesions. For PET negative IPMNs, surgery was performed only when clinical and radiologic features suggested malignancy or the patients were young. A lesion >3 cm, the presence of mural nodules and thick wall, the dilation of MPD >1 cm, high serum levels of CA 19-9, recent-onset of diabetes and jaundice were considered related to potential malignancy, as previously reported.4,20 Standard resection was the operation of choice for malignancies, whereas type 3 duodenum preserving pancreatic head resection,21 median pancreatectomy, enucleation, or spleen preserving surgery was reserved for benign or borderline lesions. The pancreatic surgical margins were analyzed intraoperatively by frozen section; negative resection margins were needed for conservative surgery. Follow-up was planned for PET negative patients when old and asymptomatic, or high surgical risk, or with lesions located in the head or in the entire gland.

RESULTS

The clinicopathologic features of the 64 patients enrolled in this study are detailed in Table 1. There were 33 males and 31 females with a mean age of 64 years (range,
A total of 13 patients were diabetic (4 IDD) and 11 presented with high serum levels of CA 19–9 tumor marker. Mean tumor diameter was 3.2 cm (range, 1.0–10.0 cm). The CT scan showed a lobulated cystic mass (n = 9), multiple cysts (n = 10), dilated MPD (n = 19) with mural nodules (n = 10). Clear CT features of malignancy were found in 15 patients (58%). Twenty-four of the 26 patients (92%) showed 18-FDG PET uptake with an SUV range of 2.5 to 9.0, mean 4.2. A focal uptake was found in 20 patients and a peripheral uptake with central absence of metabolism was found in 4; 18-FDG PET also showed hepatic metastases in 2 of 24 patients, and a lymph node metastasis was not seen by conventional imaging in 1 of 24. Thirteen patients underwent pylorus-preserving pancreaticoduodenectomy (PPPD), 2 total pancreatectomy (TP), 7 distal pancreatectomy (DP) and splenectomy, 2 biliary and gastric bypass. The 2 patients with hepatic metastases demonstrated by 18-FDG PET did not undergo surgery; the diagnosis was confirmed by percutaneous fine-needle biopsy.

Pathologic diagnosis showed 21 invasive cancers (2 metastatic) and 5 noninvasive (in situ) carcinomas. 18-FDG PET showed an increased uptake in 4 of 5 carcinomas in situ (80%) and in 20 of 21 invasive cancers (95%) (Table 2): all the 5 asymptomatic patients showed a pathologic uptake of 18-FDG and were resected. The 2 false negative PET patients were a woman with recurrent attacks of acute pancreatitis with a 2-cm-cyst in the head of the pancreas and a carcinoma in situ (CT and MR features negative for malignancy), and a man with invasive malignant IPMN of the head of the pancreas with solid component at CT examination, suggesting malignancy. Conventional imaging techniques showed clear or equivocal signs of malignancy in 2 of 5 (40%) carcinomas in situ and in 13 of 21 (62%) invasive cancers.

**Benign Neoplasms**

Among the patients with benign neoplasms, there were 18 males and 20 females with a mean age 62 years (range, 37–80 years) (Table 1). Sixteen patients (42%) were asymptomatic: the most common symptoms were abdominal pain (n = 27) with one or more attacks of acute pancreatitis (n = 15), jaundice (n = 7), malabsorption (n = 1), gastrointestinal hemorrhage (n = 1), and cholangitis (n = 1). A total of 13 patients were diabetic [6 Insulin Dependent Diabetes (IDD)]. The final pathologic diagnosis was obtained by pathologic review of the surgical specimen in 44 patients, percutaneous biopsy in 2, and brush cytology during endoscopic retrograde cholangiopancreatography in 1. Twenty-six patients had malignant neoplasms: 5 carcinomas in situ, 21 invasive carcinoma. Twenty-one patients had a benign neoplasm proven by histology. One of them and 17 patients considered to have benign disease without histology were put on follow-up. Mean tumor diameter was 2.8 cm (range, 1.0–10.0 cm). Forty-one patients had multiple pancreatic cystic lesions. The main tumor arose from a branch duct in 36 patients, and from the MPD in 28 patients.

### Malignant Neoplasms

There were 15 males and 11 females with a mean age of 65 years (range, 41–81 years) (Table 1). Twenty-one patients (80.77%) were symptomatic: 9 had abdominal pain, 7 had jaundice, 4 had one or more attacks of acute pancreatitis, and 1 was presented with steatorrhea. One of the jaundiced patients with a diagnosis of chronic pancreatitis underwent biliary and pancreatic endoprosthesis before referral to our department. Five patients were asymptomatic and their lesion was incidentally found during investigation or follow-up for other disease (chronic hepatitis 2, prostate cancer 1, trauma of the hip 1, and high serum CA 19–9 levels 1). Eight patients were diabetic (4 IDD) and 11 presented with high serum levels of CA 19–9 tumor marker. Mean tumor diameter was 3.2 cm (range, 1.0–10.0 cm). The CT scan showed a lobulated cystic mass (n = 9), multiple cysts (n = 10), dilated MPD (n = 19) with mural nodules (n = 10). Clear CT features of malignancy were found in 15 patients (58%). Twenty-four of the 26 patients (92%) showed 18-FDG PET uptake with an SUV range of 2.5 to 9.0, mean 4.2. A focal uptake was found in 20 patients and a peripheral uptake with central absence of metabolism was found in 4; 18-FDG PET also showed hepatic metastases in 2 of 24 patients, and a lymph node metastasis was not seen by conventional imaging in 1 of 24. Thirteen patients underwent pylorus-preserving pancreaticoduodenectomy (PPPD), 2 total pancreatectomy (TP), 7 distal pancreatectomy (DP) and splenectomy, 2 biliary and gastric bypass. The 2 patients with hepatic metastases demonstrated by 18-FDG PET did not undergo surgery; the diagnosis was confirmed by percutaneous fine-needle biopsy.

### TABLE 1. Clinical and Pathologic Characteristics of the 64 Patients Investigated

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Total</th>
<th>Malignant</th>
<th>Benign</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>Mean</td>
<td>63.6</td>
<td>65.0</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>37–84</td>
<td>41–81</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>33</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>31</td>
<td>11</td>
</tr>
<tr>
<td>Treatment</td>
<td>Resection</td>
<td>42</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>Bypass</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Observation</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Yes</td>
<td>37</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>27</td>
<td>5</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Yes</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>51</td>
<td>18</td>
</tr>
<tr>
<td>Ca 19-9 (&gt;37 U/mL)</td>
<td>16</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Subtype</td>
<td>Main duct</td>
<td>28</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Branch duct</td>
<td>36</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Mural nodules</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Pancreatic duct dilation</td>
<td>36</td>
<td>21</td>
</tr>
<tr>
<td>Mean size (cm)</td>
<td>2.8</td>
<td>3.2</td>
<td>2.6</td>
</tr>
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</table>

**TABLE 2. Imaging and PET Results According to Pathologic Features**

<table>
<thead>
<tr>
<th>Pathology</th>
<th>N</th>
<th>Pos</th>
<th>Neg</th>
<th>PET</th>
<th>CT/MR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenoma</td>
<td>13</td>
<td>0</td>
<td>13</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>Borderline</td>
<td>8</td>
<td>1*</td>
<td>7</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Ca in situ</td>
<td>5</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>21</td>
<td>20</td>
<td>1</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>Undetermined</td>
<td>17</td>
<td>0</td>
<td>17</td>
<td>3*</td>
<td>14</td>
</tr>
<tr>
<td>Total</td>
<td>64</td>
<td>25</td>
<td>39</td>
<td>23</td>
<td>41</td>
</tr>
</tbody>
</table>

*Patient with associated colon carcinoma.

*Two patients with equivocal radiological features of malignancy.
and cholangitis (n = 1). Five patients were with diabetes (2
IDD) and 5 presented with increased CA 19–9 levels.
Twenty-two patients (58%) were asymptomatic and their
lesion was incidentally found during investigations for
unrelated disease. CT and/or MR showed a lobulated
cystic mass in 9 patients, multiple cysts in 23, and a
marked dilation of MPD in 6 patients. The dilation of the
MPD was associated to cystic lesion in a total of 15
patients. The main tumor diameter was 2.6 cm (range,
1.0–10.0 cm). Seven patients (18%) showed CT or MR
features suggesting a malignant tumor (solid component or
mural nodules). In 37 of 38 patients (97%) no pathologic
uptake of 18-FDG was shown. The remaining patient
showed a focal uptake in the head of the pancreas (SUV
uptake of 18-FDG was shown. The remaining patient
mural nodules). In 37 of 38 patients (97%) no pathologic
1.0 –10.0 cm). Seven patients (18%) showed CT or MR
patients. The main tumor diameter was 2.6 cm (range,
MPD was associated to cystic lesion in a total of 15
2.5) corresponding to very small mural nodules within
cystic lesion and MPD dilation at CT and MR examina-
tions. A focal uptake of 18-FDG was detected also in the
right colon: colonscopy showed a polipoid mass. A TP and
right colectomy were performed; pathology showed a
diffuse borderline IPMN of the pancreas and a carcinoma
in situ of the right colon.

Twenty patients underwent resection: PPPD (3), pylo-
rus-preserving TP (2), type 3 duodenum preserving pancreatic
head resection21 (3), median pancreatectomy (1), enucle-
ation (2), and spleen-preserving DP (9). Eighteen patients
considered harboring a benign disease were put on follow-up;
only 1 of them underwent brush cytology during endoscopic
retrograde cholangiopancreatography with a pattern compat-
ible with adenoma. Three (77, 77, and 78 years old) of the 18
patients were CT scan positive and 18-FDG PET negative; 1
refused surgery and 2 were considered at high risk due to
associated diseases. All patients were followed as described
(mean and median follow-up 25 and 27.5 months, respecti-
tively; range, 12–90 months); none of them showed malign-
ancy or substantial changes in the radiologic appearance of
their lesion. The final pathologic diagnosis was adenoma in
13 patients, borderline tumor in 8, and remained undeter-
mined in 17 nonoperated patients (Table 2).

Sensitivity, specificity, PPV, NPV, and accuracy of
18-FDG PET in detecting malignant IPMNs were 92%, 97%,
96%, 95%, and 95%; these figures for CT and/or MR were
58%, 82%, 68%, 74%, and 72%; if only patients with proven
histology are considered, the corresponding figures were
92% versus 58%, 95% versus 81%, and 94% versus
68%. There are few reports dealing with PET imaging and
IPMNs of the pancreas. In 2001, we reported a better accu-
cacy of 18-FDG PET than CT in detecting malignant IPMNs. If only patients with
proven histology are considered, the corresponding figures were 92% versus 58%, 95% versus 81%, and 94% versus
68%. There are few reports dealing with PET imaging and
IPMNs included.17 The results were confirmed in 2005 on further 50 patients, 17
IPMNs included.18 In 2003, Yoshioka et al22 reported a high
18-FDG uptake in 2 patients with IPMN and invasive carci-
noma. In the same year, McHenry et al23 reported that EUS
fine needle aspiration biopsy was more accurate (71%) than
PET scan (50%) in detecting malignant cystic lesions in 13
patients, 8 IPMNs (3 benign and 5 malignant) included.
Unfortunately, this study was published only as an abstract,
and the procedure of the 18-FDG PET was not clearly
described. The authors suggested the need of further experi-
ences to assess the role of 18-FDG PET in pancreatic cystic
lesions. More recently, Mansour et al24 of the Memorial Sloan-Kettering Cancer Center of New York, investigated 68
patients with suspected cystic tumors of the pancreas (5
IPMNs) with PET scan, and reported that the sensitivity
(57%) and specificity (85%) of PET for malignancy was
much lower than previously reported by our group.17,18 Un-
fortunately, only 21 patients (29%) were resected and, among
them, only 8 had malignant lesions. Furthermore, only 5
patients had an IPMN (3 benign and 2 malignant), and the
18-FDG PET was performed in only 4 (3 negative and 1
positive). Finally, the procedure of the 18-FDG PET was not
reported. We should remember that the results of 18-FDG
PET depend on several factors, procedure and instrumenta-
tion included.25

In recent years, 18-FDG PET imaging has been increas-
ingly used in the diagnosis, staging, and post-treatment sur-
veillance of many types of malignancies.10 During the pro-

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**FIGURE 1. Treatment tree of the 64 IPMNs.**

**DISCUSSION**

This is the largest study performed on the role of
18-FDG PET in IPMNs. The present study demonstrated a
better sensitivity (92% vs. 58%), specificity (97% vs. 82%),
and accuracy (95% vs. 72%) of 18-FDG PET than CT and
MR in detecting malignant IPMNs. If only patients with
proven histology are considered, the corresponding figures were
92% versus 58%, 95% versus 81%, and 94% versus
68%.
cess of malignant transformation, the majority of cells become avid glucose scavengers, with increased glucose transport and utilization. The enhanced glucose uptake explains why 18-FDG PET can functionally identify malignant tissue. This principle led us to verify in 2001\textsuperscript{17} and 2005\textsuperscript{18} a possible role of 18-FDG PET in the differential diagnosis of cystic lesions of the pancreas, particularly in distinguishing malignant from benign pancreatic cystic tumors. In both studies, 18 FDG PET showed a better accuracy in detecting malignant cysts compared with conventional imaging techniques, and the results were confirmed by histology in 55 of 56 patients of the first study\textsuperscript{17} and in 35 of 50 of the second study.\textsuperscript{18} In the present study, the 26 IPMN patients of the previous studies were also included and histology was confirmed in 47 of 64 patients. The accuracy of the procedure was therefore verified by histology in a total of 116 of 144 patients.

In our study, 18-FDG PET was able to detect 24 of 26 malignant IPMNs (sensitivity 92%), and, among them 4 of 5 patients with a carcinoma in situ; in 3 of these patients CT and MR did not show any sign of malignancy. Furthermore, 18-FDG PET added new information about tumor extension in 2 of 26 patients, showing hepatic metastases not detected by traditional imaging. The false negative results occurred in a patient with IPMN and carcinoma in situ (not seen also by traditional imaging) and in a jaundiced patient with invasive IPMN carcinoma of the head of the pancreas correctly detected by CT scan. The recent International Association of Pancreatology guidelines for the management of IPMN of the pancreas stated that, at present, it is impossible to diagnose preoperatively the minimal invasion of IPMN as is the case in minimally invasive MCN.\textsuperscript{26} If we consider that 18-FDG PET was positive in 4 of 5 of our patients, and in the 80-year-old female with IPMN in situ reported by Mansour et al,\textsuperscript{24} it may be considered a promising diagnostic test for minimally invasive IPMNs.

In our study, only 1 of 38 patients with benign lesions was PET positive (specificity, 97%); a simultaneous focal uptake of 18-FDG was shown in the right colon, and the patient underwent a TP and right colectomy. Pathology showed a main duct diffuse borderline IPMN and a carcinoma in situ of the right colon. Considering all the patients with benign lesions who underwent 18-FDG PET for cystic lesions in our department, only 4 of 110 were PET positive (specificity 96%).

Cystic lesions of the pancreas, IPMNs included, are increasingly recognized, often entirely asymptomatic, because of the increasing use of high quality cross-sectional imaging.\textsuperscript{27} IPMNs are considered a premalignant precursor to pancreatic adenocarcinoma; so, surgical resection is advocated for these lesions. However, the time and the real incidence of progression from benign to frankly malignant tumor is very difficult to be defined,\textsuperscript{28} and a difference in potential malignancy between main duct and branch duct type IPMNs, has been reported.\textsuperscript{29,30} Furthermore, an increasing number of asymptomatic patients with IPMN are now detected, and, frequently, these neoplasms are discovered in people over age 70 and 80 with comorbidities that make surgical resection less desirable. Finally, the resection of neoplasms located in the head or diffuse to all pancreas suggests caution even in younger patients, especially if alternative pancreas sparing procedures are available for benign or borderline disease. Such an approach might be applied with more confidence if reliable preoperative indicators of malignant versus benign neoplasms exist. Therefore, we need a simple, reliable, and noninvasive test that is able to differentiate malignant from benign IPMN.

Despite previous reports of typical clinical and radiologic features, conventional imaging modalities, such as CT and MR do not reliably distinguish between benign and malignant IPMNs.\textsuperscript{8,11,12} In our experience, the accuracy of CT and/or MR in detecting malignant IPMNs was 72%, with sensitivity and a specificity of 58% and 82%. It was only slightly lower (accuracy 68%, sensitivity 58%, specificity 81%) if only histologically proven lesions are considered. The sensitivity and specificity of CT and MR for malignant cystic lesions have been reported as 25% to 100% and 40% to 92%.\textsuperscript{24}

EUS has an expanding role in the preoperative evaluation of pancreatic neoplasms, including IPMNs,\textsuperscript{9,31} but EUS alone seems not to substantially improve CT results in distinguishing malignant from benign lesions.\textsuperscript{10,13} Furthermore, EUS is a highly operator dependent procedure, and a large experience is needed before reaching satisfactory results. EUS fine-needle aspiration cytology seems to be a logical adjunctive test to better define a malignant cystic mass of the pancreas.\textsuperscript{32} However, cytology often shows false negative or inconclusive results, and only presence of atypia has been suggested as reliable indicator of malignancy.\textsuperscript{33} Wiesnauer et al\textsuperscript{3} emphasized the usefulness of cytologic sources (ductal lavage, brushing, FNA) in detecting malignant IPMNs with a sensitivity of 91%. However, only 40% of noninvasive cancers (ie, carcinoma in situ) were detected by examination of cytologic specimens.

Our surgical policy changed with increasing experience with PET-scan. Although we started resecting with standard procedures (PD, PPPD, TP, and DP) most of our IPMNs, nowadays we perform type 3 duodenum preserving pancreatic head resection,\textsuperscript{21} median pancreatectomy, or spleen preserving surgery whenever possible (Fig. 1), and propose a wait and see policy to patients with PET negative branch duct IPMNs, and also for older (>70 or 80 years) or high risk patients with a PET negative main duct IPMN. According to this policy, a negative PET-scan prompted a more conservative pancreatic resection (n = 6) or avoided unnecessary splenectomy (n = 9).

Furthermore, 18 patients underwent follow-up. All nonoperated patients were checked at 6 months, and thereafter once a year. None showed changes in cyst diameter or appearance. Although the follow-up is relatively short (mean and median follow-up 25 and 27.5 months, respectively; range, 12–90 months) it is in the range of that reported by others.\textsuperscript{4,12,24} Finally, positive 18-FDG PET findings influenced surgical decision making in 10 patients (16%) suggesting surgical resection in 7 patients (2 asymptomatic) without signs of malignancy on conventional imaging, allowing resection of a borderline IPMN associated with an unsuspected colon can-
cer in 1 patient, and avoiding laparotomy in 2 patients with hepatic metastases not seen by CT. Negative 18-FDG PET allowed planning follow-up strategy for 3 patients with CT-positive lesion.

CONCLUSIONS

18-FDG PET is a very useful technique for the preoperative work-up of patients with suspected IPMNs of the pancreas. It is much more accurate than conventional imaging in distinguishing benign from malignant lesions, including noninvasive carcinomas. 18-FDG PET is better than other imaging techniques in selecting IPMNs patients, especially asymptomatic, for surgical treatment or for long-term follow-up.

ACKNOWLEDGMENTS

The authors thank Tania Lazzarin for helping with the manuscript.

REFERENCES


Discussions

PROFESSOR K. CONLON: We have heard from this presentation and the previous presentation that the diagnosis of intraductal papillary mucinous tumors is problematic and the treatment is somewhat controversial. In addition, a significant proportion of patients, up to 50%, irrespective of whether or
not main or branch ducts are involved will either harbor invasive cancer or in situ disease. I have a number of specific questions.

First, I would like you to expand on your criteria for CT assessment of these patients. I am somewhat unclear from your presentation as to what would make you, on the basis of the CT alone, adopt a conservative approach. For the 2 examples you showed in this presentation, if I saw them in my clinic, I would take them to the operating theater.

My second question relates to the actual CT technology used in your study. You have shown us 2 types of CT technology – the helical scanner before 2004 and the multisliced integrated PET scanner from 2004 onward. Was there any difference in the results from these differing technologies?

My third question addresses the role of PET scanning in the follow-up of this group of patients. Do you have any experience using PET scanning in follow-up?

PROFESSOR S. PEDRAZZOLI: Perhaps the images that were chosen are not the best, but our criteria were tumor diameter <3 cm mural nodules less than 10 mm. There is a debate as to whether the lower limit of the size of mural nodules should be considered potentially malignant; several limits have been proposed: 6, 7, 8, 9, and 10 mm. So we used the criteria defined by previous authors. I admit that we saw referred patients coming from several places, and the CT scan was not always of good quality, so the result may not be as good as if performing them following the same procedure and using the same scanner. But I believe that it is important for general surgeons to understand that accuracy is not higher than 60% to 75%, and that is quite a bit lower than >90% with the 18-FDG PET.

As for your second question about PET scan and the PET CT scan, we did not see any difference between the two. Here is an example of a more recent case regarding follow-up. A female patient of 82 years was put on follow-up because of a negative PET. One year later the PET scan became positive. I was convinced, it was cancer although no PET CT scan on these patients without CT at all?

PROFESSOR S. PEDRAZZOLI: Thirty-one were CT and PET negative. Fifty-six percent of the 16 resected patients were symptomatic. Only 1 was malignant.

PROFESSOR K. CONLON: So it is symptoms, then?

PROFESSOR S. PEDRAZZOLI: Yes, for 56%.

PROFESSOR P.-A. CLAVIEN: This is a clinically significant topic with the aim of identifying the timing and maybe the type of surgery for this difficult population of patients. I have, however, a concern regarding the design of the study, which is reflected in the title of your presentation: “18-FDG PET is much better than CT in distinguishing benign from malignant IPMN of the pancreas”. Currently, we do not want to compare PET scanning with CT, but rather the combined PET/CT versus CT alone. I understand that many patients in your study had a PET scan alone followed by a CT scan, but today the PET machine without a combined CT is no longer available. The industry is producing only PET/CT, in which CT can be performed with or without IV contrast.

PROFESSOR S. PEDRAZZOLI: Are you speaking about PET CT with or without contrast?

PROFESSOR P.-A. CLAVIEN: Most of us today will get a PET/CT using IV contrast. With this tool we have the full information from the CT scanning plus the exact anatomic information of the positive PET lesions. But I would formulate my question as follows: “Today would you do just a PET scan on these patients without CT at all?”

PROFESSOR S. PEDRAZZOLI: No.

PROFESSOR P.-A. CLAVIEN: Therefore, the relevant question that needs to be addressed using your important data is whether PET plus a CT scan is superior to the CT scan alone. In other words, does the addition of the PET enable the detection of more tumors and their dignity? We want to be better in detecting malignant versus benign lesions in IPMN patients.

PROFESSOR S. PEDRAZZOLI: The diagnosis of IPMN does not need PET scan, but certainly PET scan is much better than CT alone to identify a malignant IPMN. The main problem in premalignant IPMNs is to be able to detect malignant changes when they occur. Malignant IPMN needs a pancreatic resection even if the surgical risk is increased, while the same patient with still benign, although premalignant, lesion may be put on follow-up. The addition of PET, with its very high accuracy, is of great aid in the decision making process.

PROFESSOR M. BUCHLER: Regarding clinical reliability and relevance, Helmut Friess, my coworker, has already published, in 1990, about PET and pancreatic cancer. This is now 17 years ago. Then, we had a sensitivity and specificity of the PET for pancreatic cancer that was around 85%. And then there were multiple trials after and, more or less, the sensitivity and specificity for the malignancy is...
around 80% but not better. So it is hard to believe that, in the IPMN situation, it should be better than 80%. Our experience is that you still have many cases where you see a false positive or a false negative and we will not rely on it.

Professor S. Pedrazzoli: You remember that there are 2 ways for pancreatic cancer to present. One is IPMN, the other is PANIN, and perhaps, there is a difference in their glucose uptake. We can have an uptake in route 1 (IPMN) that is much higher than in route 2 (PANIN and pancreatic cancer) and this may be an explanation as to why, because we now have 144 cystic lesions with an accuracy that remains over 90%. It has remained so for 7 years. One hundred sixteen of 144 have histology. It may be by chance, but I do not believe so with such a number.
Use of Severely Steatotic Grafts in Liver Transplantation
A Matched Case-Control Study

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Background: Although there is a worldwide need to expand the pool of available liver grafts, cadaveric livers with severe steatosis (>60%) are discarded for orthotopic liver transplantation (OLT) by most centers.

Methods: We analyzed patients receiving liver grafts with severe steatosis between January 2002 and September 2006. These patients were matched 1:2 with control patients without severe steatosis according to status the waiting list, recipient age, recipient body mass index (BMI), and model for end-stage liver disease (MELD) score. Primary end points were the incidence of primary graft dysfunction (PGF), and graft and patient survival. Secondary end points included primary graft dysfunction (PDF), the incidence of postoperative complications, and histologic assessment of steatosis in follow-up biopsies. We also conducted a survey on the use of grafts with severe steatosis among leading European liver transplant centers.

Results: During the study period, 62 patients dropped out of the waiting list and 45 of them died due to progression of disease. Of 118 patients who received transplants 20 (17%) received a graft with severe steatosis during this period. The median degree of total liver steatosis was 90% (R = 65%–100%) for the steatotic group. The steatotic (n = 20) and matched control group (n = 40) were comparable in terms of recipient age, BMI, MELD score, and cold ischemia time. The steatotic group had a significantly higher rate of PDF and/or renal failure. Although the median intensive care unit (ICU) and hospital stay were not significantly different between both groups, the proportion of patients with long-term ICU (=21 days) and hospital (=40 days) stay was significantly higher for patients with a severely steatotic graft. Sixty-day mortality (5% vs. 5%) and 3-year patient survival rate (83% vs. 84%) were comparable between the control and severe steatosis group. Postoperative histologic assessment demonstrated that the median total amount of liver steatosis decreased significantly (median: 90% to 15%, P < 0.001). Our survey showed that all but one of the European centers currently reject liver grafts with severe steatosis for any recipient.

Conclusion: Due to the urgent need of liver grafts, severely steatotic grafts should be no longer discarded for OLT. Maximal effort must be spent when dealing with these high-risk organs but the use of severely steatotic grafts may save the lives of many patients who would die on the waiting list.

Over time, outcome after liver transplantation has been markedly improved due to new effective immunosuppressive agents, advances in surgical techniques, improved perioperative care, and better management of postoperative complications. These improvements and the lack of cadaveric donors in Switzerland, a country with a high incidence of liver diseases and no coverage until recently for living donation, forced us to consider all steatotic livers suitable for OLT. We report our experience with the use of grafts with severe steatosis and performed a survey among leading European transplant surgeons to evaluate current policy regarding those organs.

METHODS

Due to the lack of cadaveric donor organs in our country associated with a dramatic increase in death on our waiting list, we decided to consider all severely steatotic grafts for OLT since January 2002. We analyzed the outcome of patients who received a severely steatotic graft compared with a group of matched control patients from a prospective database. Our allocation policy established in 2002 was to use severely steatotic livers exclusively in lower risk recipients (model for end-stage liver disease (MELD) ≤24) or in patients with acute liver failure (ALF). Donor graft biopsies were selectively performed in the presence of any macroscopic or sonographic sign of steatosis. A core needle biopsy was performed and acceptance of such liver grafts was decided only after histologic evaluation of the donor biopsy. Severe steatosis was defined as presence of fat droplets in more than 60% of hepatocytes in the pretransplant allograft biopsy. All 20 patients with severely steatotic grafts were matched with 40 control patients (1:2) who were transplanted during the same period with grafts having normal appearance or displaying no severe steatosis on histology of the liver biopsy in terms of the following matching criteria: status in the waiting list (elective vs. high urgent), recipient age ± 10 years, recipient body mass index (BMI) (normal weight BMI ≤25 kg/m² vs. overweight BMI 25–29 kg/m² vs. obese BMI ≥30 kg/m²), and MELD score ± 5. Primary end points were mortality, PN, and graft survival. PN was defined as death or retransplantation within 7 days after OLT in the absence of any vascular problems. Secondary end points were primary dysfunction of the graft (PDF), the incidence of postoperative complications and histologic assessment of steatosis on follow-up liver biopsies in patients with severe steatosis. PDF was defined when a peak of aspartate aminotransferase (AST) level >1.500 IU/L and a prothrombin time ≤50% coexisting within the first week.¹³,¹⁶

Donor Data

Organ procurement was performed as described elsewhere with aortic and portal perfusion using University of Wisconsin preservation solution (Viaspan; DuPont, Wilmington, DE).¹⁷ In agreement with others,¹¹,¹³,¹⁸,¹⁹ the following marginal donor criteria were recorded in addition to severe steatosis: cardiac arrest >15 minutes or prolonged hypotensive episodes of <60 mm Hg for >1 hour, donor age >55 years, high vasopressor drug requirement (dopamine dose >10 μg/kg/min or any doses of other amines), hypernatremia >155 mEq/L, prolonged intensive care unit (ICU) stay (≥5 days with mechanical ventilation), elevated liver transaminases (AST >170 U/L or ALT >140 U/L), and prolonged cold ischemia (>12 hours). Additionally, the BMI of each donor was assessed. Donor obesity was defined as BMI ≥30 kg/m².

Histologic Evaluation

Each biopsy of severely steatotic grafts was blindly re-evaluated by a single experienced pathologist (WJ) using hematoxylin and eosin (H&E) stained sections of formalin-fixed paraffin-embedded liver tissue. The following variables were assessed: degree and type of steatosis, fibrosis and portal inflammation. Steatosis was further characterized into macro (MaS) and microvesicular (MiS) steatosis. Liver fibrosis was quantified according to the METAVIR scoring system using Sirius red stained sections.²⁰ Portal inflammation was graded as mild, moderate or severe.

Recipient Data

All transplants were performed without veno-venous bypass, as previously described.¹⁷ In 1 patient with amyloidosis, the liver was used for a second recipient (domino OLT). The following recipient data were collected: age, underlying liver disease, MELD score, BMI, recipient status on the waiting list (elective, emergency), surgical technique, transfusion requirement, operative time and immunosuppressive regimen.

Postoperative Outcome

Liver allograft function was evaluated clinically and through biochemical parameters such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin and prothrombin time measured preoperatively and daily until discharge. Complications grades 3 to 5 (ie, requiring surgical intervention, ICU admission or death, respectively) were recorded according to our classification system for postoperative complications.²¹ Liver biopsies during follow-up were only obtained in each patient with abnormal liver parameters. After discharge, each patient was followed in our multidisciplinary outpatient clinic.

Questionnaire

We conducted a survey with expert transplant surgeons participating in the 2006 Annual Meeting of the European Surgical Association (Zurich, April 2006) to evaluate their attitude towards steatotic grafts. Responders represented leading liver transplant programs from Germany (n = 6), Netherlands (n = 2), Belgium (n = 1), France (n = 3), United Kingdom (n = 1), Austria (n = 1), and Finland (n = 1) (see appendix).

Statistical Analysis

Summary data are presented as median (range) or mean ± SD. Differences between groups were tested by χ² test for categorical and Mann-Whitney U test for continuous variables. Patients and grafts survival was analyzed by the Kaplan-Meier method. The outcome event for patient survival was “death” or “alive” and for graft survival “graft failure” or “no graft failure.” Graft failure was defined as death, retransplantation, or documented cirrhosis. Compar-
isons between survival curves were performed using the log-rank test. All tests were performed two-tailed. Statistical significance was indicated by \( P \) values of less than 0.05. Calculations were done with SPSS statistical software package (version 11.5).

**RESULTS**

**Drop-out and Death on the Waiting List**

The median annual number of patients on the waiting list was 71 during the study period. During the whole study period, 62 patients dropped out of the waiting list and 45 of them died due to progression of disease and the lack of a suitable donor organ. This corresponds to a median annual drop-out rate of 26% and death rate of 17%. On the other hand, 118 patients were transplanted during this period (elective n / H11005 110, high urgent n / H11005 17). The median time on the waiting list for patients with ALF was 1.5 days (1–2), and 6 months (1–31) for those who were electively transplanted.

**Liver Grafts With Severe Steatosis Offered for Liver Transplantation**

Twenty-two livers disclosing severe steatosis were offered to our program during the study period. Two were rejected due to other associated histologic features including advanced fibrosis (METAVIR score F4) in one and severe steatohepatitis in the other. Additional risk factors in the 20 donors included in this analysis are listed in Table 1. Of note, all, but two, donors presented 1 or more other “extended criteria” for OLT. All donors were ABO-compatible with the recipient blood type.

Although 15 donors (75%) were overweight (BMI > 25 kg/m²), only 5 (25%) were obese (BMI > 30 kg/m²). Two out of 3 patients with prolonged ICU stay (10 and 12 days) had pneumonia with persistent fever despite the use of broad spectrum antibiotics for >7 days.

**Degree and Type of Severe Steatosis**

The median amount of total steatosis was 90% (range 65–100) for the severe steatosis group (n = 20). The type of liver steatosis in each patient is described in Table 1. Although no graft had lobular inflammation suggesting steatohepatitis, graft histology revealed mild or moderate unspecific portal inflammation in 4 and 3 cases, respectively. Mild fibrosis was observed in 10 livers (F1: n = 7; F2: n = 3).

**Clinical Status of the Recipients of Severely Steatotic and the Matched Control Group**

As expected, the control and steatotic group were comparable in terms of the matched variables (status on the waiting list, recipient age, BMI, and MELD score) (Table 2). Indications for OLT in the severely steatotic group were

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**TABLE 1. Donor and Recipient Features of Each Graft With Severe Steatosis**

<table>
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<tr>
<th>No.</th>
<th>Age (yr)</th>
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<th>Risk Factors*</th>
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<th>MaS (%)</th>
<th>MiS (%)</th>
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<td>Yes</td>
<td>6</td>
</tr>
<tr>
<td>20</td>
<td>42</td>
<td>6.6</td>
<td>Vasopressor</td>
<td>90</td>
<td>50</td>
<td>40</td>
<td>44</td>
<td>HCV</td>
<td>10</td>
<td>52†</td>
<td>116</td>
<td>Yes</td>
<td>6</td>
</tr>
</tbody>
</table>

*Risk factors defined in the methods section of the manuscript.
†Patients with hepatocellular carcinoma.
‡Patients requiring hemodialysis or hemofiltration.

ALF indicates acute liver failure; CIT, cold ischemia time; ELFT, elevated liver function test; HBV, hepatitis B virus; HCV, hepatitis C virus; ICU, intensive care unit; MaS, macrosteatosis; MiS, microsteatosis; TS, total steatosis.
Portuguese Familial Amyloidotic Polyneuropathy (domino transplantation) in 1 patient, fulminant liver failure (1 toxic, 1 cryptogenic, and 1 hepatitis B virus) in 3, and the remaining 16 recipients presented with liver cirrhosis due to various causes (Table 1). Among all recipients with a severely steatotic graft (median BMI 25.5 kg/m², range 20–36), only one was obese with a BMI >30 kg/m². Elective and high urgent OLT had a comparable distribution for control and steatotic patients (34 and 6 vs. 17 and 3, P = 1.00) (Table 2). For the steatotic group, the median MELD score in the subgroup with cirrhosis (n = 16) was 12 (6–22). When corrected according to UNOS with additional points for patients with hepatocellular carcinoma according to UNOS.

### Operative Data of the Severe Steatosis Group

A piggyback technique was performed in 3 patients and the standard technique with cava resection in the others. In each recipient a full-size liver was implanted. Only 1 graft had a prolonged cold ischemia time (14 hours) and none had >40 minutes of warm ischemia time. One recipient (case 10) had an intraoperative cardiac arrest during reperfusion of the liver graft, but subsequently had an uneventful course without neurologic sequel. The mean operation time was 287 ± 37 minutes and the median red blood cells transfusion requirement was 5 units (0–17). No patient required technical adaptation to avoid intraperitoneal high pressure secondary to size mismatch among donor liver and recipient abdominal cavity.

### Early Outcome After Transplantation

Liver support therapy was not used in any recipient before or after OLT. One patient (case 6) in the steatotic group (5%) developed PNF in the absence of vascular problems (Table 3). This patient had 4 additional donor risk factors and required retransplantation on postoperative day 4 due to PNF, but died due to an uncontrolled *Staphylococcus aureus* sepsis. A peritoneal fluid culture from the first donor revealed the same bacterium, suggesting a graft contamination as the origin of the lethal sepsis. Although the cold ischemic time was similar for the control and severe steatosis group, severely steatotic liver displayed a significantly higher vulnerability to the same degree of ischemic insult demonstrated by higher median serum peak AST (847 vs. 3322 U/L, P = 0.002) and peak ALT values (865 vs. 2312 U/L, P = 0.032) (Fig. 1 and Table 3). Immunosuppressive regimen was based on tacrolimus (n = 11) or cyclosporine (n = 9). The overall severe complication rate (grade 3–5) was higher for

---

**TABLE 2.** Transplant-related Characteristics of the Control and Severe Steatosis Group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control (n = 40)</th>
<th>Severe Steatosis (n = 20)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor age (yr)</td>
<td>44 (13–71)</td>
<td>55 (26–67)</td>
<td>0.007</td>
</tr>
<tr>
<td>Recipient age (yr)*</td>
<td>51 (23–69)</td>
<td>48.5 (24–71)</td>
<td>0.826</td>
</tr>
<tr>
<td>Recipient BMI (kg/m²)*</td>
<td>25 (18–32)</td>
<td>25.5 (20–36)</td>
<td>0.474</td>
</tr>
<tr>
<td>Recipient nutritional status†</td>
<td>18/18/4</td>
<td>9/9/2</td>
<td>1</td>
</tr>
<tr>
<td>(normal/overweight/obese)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MELD*†</td>
<td>12 (6–25)</td>
<td>12 (6–22)</td>
<td>0.684</td>
</tr>
<tr>
<td>MELD corrected‡</td>
<td>18.5 (8–25)</td>
<td>24 (10–24)</td>
<td>0.228</td>
</tr>
<tr>
<td>Elective/emergency*</td>
<td>34/6</td>
<td>17/3</td>
<td>1</td>
</tr>
<tr>
<td>Cold ischemia time (min)</td>
<td>514 (186–1197)</td>
<td>562 (260–833)</td>
<td>0.855</td>
</tr>
</tbody>
</table>

Data are expressed as median (range) or number of events. *Matched variables.

---

**TABLE 3.** Early and Late Outcome of the Control and Severe Steatosis Group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control (n = 40)</th>
<th>Severe Steatosis (n = 20)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak AST (U/L)*</td>
<td>847 (131–8294)</td>
<td>3322 (461–13560)</td>
<td>0.002</td>
</tr>
<tr>
<td>Peak ALT (U/L)*</td>
<td>865 (117–7249)</td>
<td>2312 (345–4700)</td>
<td>0.032</td>
</tr>
<tr>
<td>Primary delayed-function (%)</td>
<td>4 (10)</td>
<td>6 (30)</td>
<td>0.05</td>
</tr>
<tr>
<td>Primary non-function (%)</td>
<td>0 (0)</td>
<td>1 (5)</td>
<td>0.721</td>
</tr>
<tr>
<td>Renal failure (%)†</td>
<td>2 (5)</td>
<td>7 (35)</td>
<td>0.002</td>
</tr>
<tr>
<td>Major complications (%)</td>
<td>10 (25)</td>
<td>8 (40)</td>
<td>0.230</td>
</tr>
<tr>
<td>Median ICU stay (d)</td>
<td>2 (1–22)</td>
<td>3 (1–52)</td>
<td>0.091</td>
</tr>
<tr>
<td>ICU stay ≥ 21 d (%)</td>
<td>1 (2.5)</td>
<td>4 (20)</td>
<td>0.021</td>
</tr>
<tr>
<td>Median hospital stay (d)</td>
<td>14 (7–85)</td>
<td>17.5 (7–116)</td>
<td>0.127</td>
</tr>
<tr>
<td>Hospital stay ≥ 40 d (%)</td>
<td>1 (2.5)</td>
<td>4 (20)</td>
<td>0.021</td>
</tr>
<tr>
<td>60-d mortality (%)</td>
<td>2 (5)</td>
<td>1 (5)</td>
<td>1</td>
</tr>
<tr>
<td>1-/3-yr patient survival rate (%)</td>
<td>86.4/83.2</td>
<td>95/84.4</td>
<td>0.591</td>
</tr>
<tr>
<td>1-/3-yr graft survival rate (%)</td>
<td>86.4/80.1</td>
<td>95/84.4</td>
<td>0.455</td>
</tr>
</tbody>
</table>

Data are expressed as median (range) or number of events (percentage). *Peak serum transaminases within the first week after OLT. 

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**FIGURE 1.** Postoperative hepatocyte injury (mean alanine aminotransferase and aspartate aminotransferase) and liver graft function (mean prothrombin time) assessed during the first week.
FIGURE 2. Complete post-transplant reversal of severe macrosteatosis within 16 days. Haematoxylin and eosin staining of donor biopsy (A) and follow-up biopsies at day 8 (B), and day 16 (C) after orthotopic liver transplantation.

<table>
<thead>
<tr>
<th>Questions</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routine biopsy in all grafts</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>Routine biopsy in grafts presented with “extended criteria”</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>Specific fat staining for histology</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Accept grafts with total amount of steatosis &lt;30%</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Accept grafts with total amount of steatosis 30%–60%</td>
<td>12*</td>
<td>1</td>
</tr>
<tr>
<td>Accept grafts with total amount of steatosis &gt;60%</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>Accept steatotic liver grafts with mild fibrosis F1–2</td>
<td>10</td>
<td>3</td>
</tr>
</tbody>
</table>

*Cut-off 30%, n = 3; 40%, n = 2; 50%, n = 5; 60%, n = 2.

The excellent results associated with the use of severely steatotic grafts in our center prompted us to conduct a survey among leading liver transplant programs in Europe (Table 4). Although patients with severely steatotic grafts had a higher incidence of PDF, renal failure, and major complications, the acceptance of grafts with moderate steatosis was depending on the cut-off value. In contrast, all but one of the centers reject severely steatotic livers for any recipient regardless of the type of steatosis (MaS or MiS). Although 8 centers (53%) indicated that they would put more weight on the presence of macrosteatosis in evaluating a graft with moderate steatosis, this discrimination is ignored by all other centers in the presence of severe steatosis. Grafts with mild fibrosis are accepted by most centers (77%).

**DISCUSSION**

This report challenges the current practice by most centers of discarding grafts with severe steatosis for OLT. Although patients with severely steatotic grafts had a higher incidence of PDF, renal failure, and major complications, the acceptance of grafts with severe steatosis was not significantly different between patients receiving severely steatotic grafts and matched control patients (Table 2). The excellent 1-year patient and graft survival rates (95% and 95%) with the use of such livers in our series are even superior to those reported by the United Network for Organ Sharing (UNOS) (87% and 82%) or the European Liver Transplant Registry (ELTR) (82% and 76%). Another important finding in our analysis is that severe liver steatosis is reversible after OLT. On this basis, we invite the transplant community to reconsider the negative attitude towards grafts with severe steatosis to cope with the shortage of liver grafts and to save lives on the waiting list.

Studies in the 1990s reported that transplantation of livers with severe steatosis almost invariably leads to PNF. In line with US centers, our European survey showed that almost all transplant surgeons currently discard severely steatotic grafts with a total amount of 60% steatosis or more, regardless of the morphologic type of liver steatosis or other factors (Table 4). However, when dealing with grafts with mild or moderate steatosis, the weight put in the type of steatosis varies among centers with most giving more importance on MaS. However, such discrimination appears to be ignored by all when dealing with a severe steatotic liver. This area of MiS versus MaS remains controversial. Several groups have recommended that grafts with more than 30% of MaS should not be used for OLT, whereas livers with mild MaS can be accepted when the total degree of steatosis does not exceed 60%. To be considered, this liver should additionally not be associated with other risk factors. Surprisingly, the only PNF in our series occurred in a patient receiving a severely steatotic graft presenting only with a minimal degree of MaS (case 6). Concerning grafts

**TABLE 4. Results of the Survey Conducted in 15 Leading European Transplant Centers**

<table>
<thead>
<tr>
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<th>Yes</th>
<th>No</th>
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<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Accept grafts with total amount of steatosis 30%–60%</td>
<td>12*</td>
<td>1</td>
</tr>
<tr>
<td>Accept grafts with total amount of steatosis &gt;60%</td>
<td>1</td>
<td>12</td>
</tr>
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*Cut-off 30%, n = 3; 40%, n = 2; 50%, n = 5; 60%, n = 2.

<ref>McCormack et al Annals of Surgery • Volume 246, Number 6, December 2007</ref>
with severe MiS, there are 2 conflicting reports on the use of such grafts for OLT. 9,23 Although one study suggested that livers with severe MiS can be safely used for OLT, 9 another reported a 100% PNF rate when severely steatotic grafts with MiS were used for retransplantation. 23 This discussion is rather academic as pure forms of MiS or MaS are exceptional, and therefore most series report their experience describing patients with a mixed form of steatosis. 22,24,28,29

The presence of more than 2 donor risk factors is associated with an increased incidence of graft loss and impaired survival after OLT. 6,18 The negative impact of some risk factors, such as donor age > 55 years, 24,30 prolonged graft ischemia time 31 and preexisting liver damage, 13,32 has limited the acceptance of steatotic grafts, even those with moderate or mild steatosis, in many centers. In our study, the majority of patients (60%) presented with 2 to 4 donor risk factors in addition to severe steatosis (Table 1). One recipient of an elderly donor graft with elevated transaminases developed PNF with secondary sepsis after OLT. Probably, the multifactorial insult to the donor organ resulted from the cumulative effect of various risk factors, including the use of high doses of vasopressors, high donor age, long ICU stay, and severe steatosis. Although our series represents a high-risk donor population, only 6 of 20 patients (30%) developed PDF and all except two are alive with an excellent long-term outcome. Based on experimental data 33 our policy was to keep the cold and warm ischemia times as short as possible when dealing with steatotic grafts, often by overlapping donor and recipient operation. Although a variable period of time was needed to process and evaluate the donor liver biopsy, this fact did not reflect in a longer period of cold ischemia time in these livers when compared with the control group and only 1 patient had a cold ischemia time exceeding 12 hours. This strategy might be one explanation for the successful outcome. Despite this precaution we observed dramatic postoperative transaminases increments (Fig. 1) reflecting the high vulnerability of severely steatotic liver, even to a limited ischemic insult.

How should severely steatotic livers be allocated? There are currently no guidelines for allocation of marginal donor organs. It remains under debate whether marginal organs should be allocated to high risk or low risk recipients 6,7 and those with moderate or mild steatosis, in many centers. In our study, the majority of patients (60%) presented with 2 to 4 donor risk factors in addition to severe steatosis (Table 1). One recipient of an elderly donor graft with elevated transaminases developed PNF with secondary sepsis after OLT. Probably, the multifactorial insult to the donor organ resulted from the cumulative effect of various risk factors, including the use of high doses of vasopressors, high donor age, long ICU stay, and severe steatosis. Although our series represents a high-risk donor population, only 6 of 20 patients (30%) developed PDF and all except two are alive with an excellent long-term outcome. Based on experimental data 33 our policy was to keep the cold and warm ischemia times as short as possible when dealing with steatotic grafts, often by overlapping donor and recipient operation. Although a variable period of time was needed to process and evaluate the donor liver biopsy, this fact did not reflect in a longer period of cold ischemia time in these livers when compared with the control group and only 1 patient had a cold ischemia time exceeding 12 hours. This strategy might be one explanation for the successful outcome. Despite this precaution we observed dramatic postoperative transaminases increments (Fig. 1) reflecting the high vulnerability of severely steatotic liver, even to a limited ischemic insult.

In conclusion, this study challenges the dogma that liver grafts with severe steatosis should be discarded for all recipients. Even in the presence of other donor risk factors, severely steatotic grafts should be considered for OLT, at least in low risk patients. Maximal effort must be spent in minimizing ischemia time and optimizing perioperative management when dealing with these high-risk organs.

ACKNOWLEDGMENTS

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b urg, Germany; P. Friend, John Radcliffe Hospital, Oxford, UK; K. Hockerstedt, U. C. J. Helsingfors, Helsinki, Finland; K. Jauch, Klinikum Grosshadern, Ludwig-Maximilian-University, Mfinchen, Germany; H. Tilanus, Erasmus MC, University Medical Center, Rotterdam, Netherlands.

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17. McCormack L, Selzner M, Clavien PA. The transplant operation. In: K. Jauch, Klinikum Grosshadern, Ludwig-Maximilian-University, Muinchen, Germany; P. Friend, John Radcliffe Hospital, Oxford, UK; K. Hockerstedt, U. C. J. Helsingfors, Helsinki, Finland; K. Jauch, Klinikum Grosshadern, Ludwig-Maximilian-University, Mfinchen, Germany; H. Tilanus, Erasmus MC, University Medical Center, Rotterdam, Netherlands.

Discussions

Professor R. Busuttil: As you know very well, this study from Dr Clavien and his group focuses on expanding the limited donor pool by using steatotic grafts. This is clearly a laudable goal and it extends the work that comes from your laboratory in trying to optimize all donors for usage. Now, as you mentioned so eloquently, I guess I should not have said ‘steatotic’, but ‘macrosteatotic’. In any event, we all know that steatosis has been recognized by many in the field to impact negatively on liver allograft function. However, I would submit to you that not all steatotic livers are bad — and a distinction has to be made between macro and micro steatosis. Livers with microsteatosis, even in excess of 60%, usually function quite well and we would routinely use them whereas those with macrosteatosis in excess of 30% often struggle. This difference has been confirmed in most liver transplant units in the US and, I believe, in Europe if I am not overstating. This was elegantly demonstrated by Dr Clavien’s laboratory studies, which were published last year in the Journal of Hepatology. I have several questions for the authors:

In your manuscript, only 7 of the 20 patients receiving steatotic grafts had greater than 30% macrosteatosis. Only 2 had greater than 60% macrosteatosis, whereas 18 of the 20 had greater than 30% microsteatosis. So, in your study group, microsteatosis vastly outnumbered those with significant macrosteatosis. Furthermore, the patients who were transplanted with livers that contained a large amount of microsteatosis and lesser amount of macrosteatosis had good outcomes, as you reported. I think this would be expected. However, if you reinterpret these data and place an importance predominantly on large globule fat, macrosteatosis, this would significantly change the power of
your series and, I believe, the conclusions drawn. So, could you please comment on that?

My second comment is that most of the recipients in your series had a relatively low MELD score and you commented that that was an important factor in determining the use of these grafts. If you examine only the recipients of the livers with greater than 30% macrosteatosis, the mean MELD score is less than 20. In the US, these organs are directed to recipients and the use of these in low MELD patients would be highly unlikely, because organs would be distributed first to the recipients with the highest MELD score. So I believe that this allocation of steatotic livers to low MELD score recipients, as you demonstrated in your article, would only work in a system where the organ is directed to the center and then the center is able to use their judgment as to who will use the organ and is that the situation that you are dealing with in Switzerland? So, how do you think that these organs that you have described would work in sicker patients with a higher MELD score?

Finally, an interesting area of this study was the finding of reversal of steatosis in these grafts. This is a novel finding that will warrant further investigation. Additionally, the discussion on multifactorial insults affecting a steatotic graft was of great interest. As an example, the importance of minimizing both warm and cold ischemia time in these marginal donors is fundamental and the effect of additional donor and recipient risk factors in graft and patient outcome will be an interesting area of future research.

Dr. L. McCormack: The first question relates to the controversy about macro- and micro steatosis. We have focused on this issue over the past decade in Professor Clavien’s laboratory, and more recently in our patients undergoing major liver resection. We have found in mouse and rat models of steatosis that both macro and microsteatosis negatively impact on the outcome after an ischemic insult. In other words, microsteatosis was not an irrelevant feature. We presented clinical data last year at the ESA meeting in Zurich regarding postoperative complications after major liver resection in patients with various degree of steatosis. We found that steatosis per se, regardless of the type of steatosis, was associated with a significant increase in major complications. This study appears in the June issue of Annals of Surgery. Additionally, a survey from the Oxford group involving 78 transplant surgeons in the US indicated that none would accept a liver graft disclosing more than 60% steatosis regardless of the presence of micro or macro steatosis. As reported in my presentation, we also asked 15 transplant surgeons at the ESA meeting last year about their interpretation of micro versus macrosteatosis, and all but one stated that mixed total amount of steatosis is important when considering graft with severe steatosis. From the literature, McMaster’s group in Birmingham published in 1999 a 100%-rate of primary nonfunction in 10 patients receiving grafts with more than 60% of microsteatosis.

Professor R. Busuttil: But that was retransplantation, not primary transplantation.

Dr. L. McCormack: You are right, but even in this higher risk population the data were suggesting a poor outcome related to microsteatosis. We do believe that the available data and the results of the surveys do not allow us to ignore microsteatosis when it comes to severe infiltration of the liver parenchyma.

The second question refers to the allocation rules. While in Switzerland, based on a new law, liver grafts will soon be distributed to patients based on the MELD system, organs were allocated to a center during the study period, and thus we could independently select the most appropriate recipient. I am now back in Argentina, which was the second country after the United States to use the MELD score system for allocation. However, I can still apply the policy learned at the Swiss HPB center, because no one is accepting grafts with severe steatosis, and thus I can allocate these livers to low MELD recipients. However, once these data are known and more centers may consider these organs, allocation to the most suitable recipient for this type of organ may become difficult.

Professor K. Hockerstedt: I would not say that everyone does not accept the fatty liver. You have shown that in Birmingham they do accept them. In Scandia transplant we do accept fatty livers a lot. I myself have once harvested a liver that looked like Swiss cheese. I was sure it was 100% fat and it was but, otherwise, it was rather good and the liver function tests in the donor were quite normal. I transplanted it to a PBC patient and she survived easily. It did not work too well in the first 2 weeks but that is not so bad. I would like to stress that in very doubtful donor livers you need the histology. Colleagues tend to give all kinds of answers when you ask them in person, but I am sure that not too many centers have a pathologist available at the time of the liver explantation, which usually occurs during the night. So, I would like to ask what histology staining do you use? Do you think there is any difference between how 2 pathologists estimate the fat and the macro and microsteatosis?

Dr. L. McCormack: We fully agree about the need to obtain a liver biopsy to objectively assess steatosis. For the purpose of this study, we retrospectively re-evaluated, in a blinded fashion, H&E stained sections of paraffin embedded liver core biopsies. This also enabled us to reliably determine the degree of fibrosis using Sirius red staining for collagen. In clinical practice, however, we use Sirius red stained frozen sections to evaluate grafts before transplantation. Sudan red staining for fat is added, because H&E staining alone may lead to underestimation of the degree of microvesicular steatosis and, as a consequence, of total steatosis. Alternatively,
Oil Red O staining can be used to detect microvesicular steatosis. In macrovesicular steatosis, the usefulness of these fat stains is limited because they are often associated with artifacts due to fat droplet fusion and displacement. I am not aware of a study that analyzed interobserver variability between pathologists with respect to quantification of steatosis.

Professor R. Adam: I disagree with your conclusion about the fact that we may accept fatty livers with more than 60% steatosis. You can say this for micro but I think you cannot really say this for macrovesicular steatosis. There are data in the literature that clearly show that when you transplant livers with more than 60% macrovesicular steatosis, the risk of PNF or dysfunction is around 80% and you published this recently in a review of the literature. The confusion may come when mixing micro and macrovesicular steatosis as this occurs most frequently. If you say more than 60% micro, or even 60% for cumulated micro and macro, I totally agree with you that the dogma should not be taken into account. But, for more than 60% macrovesicular, our data (and this has been confirmed by many other studies) have clearly shown that you see a high risk of dysfunction when you transplant such livers. So, if you propose to transplant diffuse microvesicular steatotic livers, I agree with you. However to say that all livers with more than 60% macrosteatosis may be transplanted, represents in my view a danger and the only 2 patients of your series transplanted in this setting do not allow you to support your conclusion. Micro, I agree. Macro, I do not.

Professor P.-A. Clavien: Thank you for clarifying this point. Our study did not establish that grafts with more than 60% macrosteatosis are safe. The data indicates that the use of grafts with mostly mixed forms of severe steatosis yields a comparable survival rate with the use of nonsteatotic livers, despite an increase in early graft injury. In our center, however, we are currently transplanting patients with macrosteatosis of more than 60%, but I agree that more data is needed to identify the limits and assess the risk. Another point is that we recently showed through a mouse model that there is continuity between micro and macrosteatosis, and we may learn that the distinction between both forms may not be as clear as usually thought. Another issue is that many of us fear moderate and severe steatosis based on an experience gathered 10 or more years ago, and consequently, have discarded these organs. Our results are currently much better, and I believe it is time to reconsider our policy to discard these organs.

Professor H. Bismuth: I think it is very important when you say not to discard steatotic livers per se. Of course, you say that you have some selection. But it is clinical selection. So, be more provocative. Do you need the liver biopsy? You said that most of the teams undertake liver biopsy to select the graft but you do not need that, according to your criteria. Would you also discard the biopsy?

Dr. L. McCormack: As mentioned earlier, we believe that a biopsy should be performed routinely when suspecting a significant amount of steatosis. Additionally, we perform biopsies not only to determine the degree of steatosis, but also to identify pathologic alterations in the graft, which we consider as contraindications for use of these organs for transplantation, eg, steatohepatitis and severe fibrosis. In our series, we discarded 2 out of 22 livers after biopsy due to the presence of steatohepatitis and grade 4 fibrosis.

Professor Buechler: I have just a final comment. I must take Pierre’s argument. I think he has encouraged us much and we have to take his series seriously. We, in Heidelberg, have ignored microvesicular steatosis for 2 years, but we still take the macrovesicular steatosis very seriously and we stop transplanting organs at 40% macrosteatosis. In the future, we will try to incorporate Pierre’s arguments more. I think that it is time to rethink the steatosis criteria for liver transplantation.

Professor P.-A. Clavien: It is surprising that we still lack conclusive data despite the high prevalence of liver steatosis in our donor population and the recognition by many that steatosis is an important risk factor for surgery and transplantation. The main reason for this shortcoming is that we failed to include steatosis or other histologic changes in our large databases, such as the UNOS or ELTR registries. Therefore, the emerging consensus based on the analysis of those registries, suggesting that “higher risk” or “marginal” organs benefit only the sickest recipients with a high MELD score, may not apply for grafts displaying severe steatosis. In fact, our data suggest that these organs may be suitable only in recipients who tolerate a first hit. Patients with very poor liver reserve do not tolerate poor initial function. Our observation that severe steatosis resolves rapidly after transplantation suggests that the use of these organs may not be associated with long-term negative impact. However, this will need further follow-up. To move on, we urgently need to include data on steatosis in our multicenter databases. Only the availability of this material will enable us to conclusively quantify the risk associated with the presence and the type of steatosis.
Background: Hepatic epitheloid hemangioendothelioma (HEHE) is a rare low-grade vascular tumor. Its treatment algorithm is still unclear mainly due to a lack of larger clinical experiences with detailed long-term follow-up.

Material and Methods: Fifty-nine patients, reported to the European Liver Transplant Registry, were analyzed to define the role of liver transplantation (LT) in the treatment of this disease. Eleven (19%) patients were asymptomatic. Eighteen (30.5%) patients had extrahepatic localization before or at the time of LT. Follow-up was complete for all patients with a median of 78.5 (range, 1–245) from the moment of LT.

Results: HEHE was bilobar in 96% of patients; 86% of patients had more than 15 nodules in the liver specimen. Early (<3 months) and late (>3 months) post-LT mortality was 1.7% (1 patient) and 22% (14 patients). Fourteen (23.7%) patients developed disease recurrence after a median time of 49 months (range, 6–98). Nine (15.3%) patients died of recurrent disease and 5 are surviving with recurrent disease. One-, 5-, and 10-year patient survival rates from moment of transplantation for the whole series are 93%, 83%, 72%. Pre-LT tumor treatment (n = 18) (89%, 89%, and 68%) and 10-year survival rates from moment of LT vs. 95%, 80%, and 73% in case of absence of pre-LT treatment, lymph node (LN) invasion (n = 18) (96%, 81%, and 71%) 1-, 5-, and 10-year survival rates vs. 83%, 78%, and 67% in node negative patients) and extrahepatic disease localization (n = 10) (90%, 80%, and 80%) 1-, 5-, and 10-year survival rates vs. 94%, 83%, and 70% in case of absence of extrahepatic disease) did not significantly influence patient survival whereas microvascular (n = 24) (96%, 75%, 52% 1-, 5-, and 10-year survival vs. 96%, 92%, 85% in case of absence of microvascular invasion) and combined micro- and macrovascular invasion (n = 28) (90%, 72%, and 54%) 1-, 5-, and 10-year survival vs. 96%, 92%, and 85% in case of absence of vascular invasion, P = 0.03) did. Disease-free survival rates at 1, 5, and 10 years post-LT are 90%, 82%, and 64%. Disease-free survival is not significantly influenced by pre-LT treatment, LN status, extrahepatic disease localization, and vascular invasion.

Conclusions: The results of the largest reported transplant series in the treatment of HEHE are excellent. Preexisting extrahepatic disease localization as well as LN involvement are not contraindications to LT. Microvascular or combined macro-microvascular invasion significantly influence survival after LT. LT therefore should be offered as a valid therapy earlier in the disease course of these, frequently young, patients. Recurrent (allograft) disease should be treated aggressively as good long-term survivals can be obtained. Long-term prospective follow-up multicenter studies as well as the evaluation of antiangiogenic drugs are necessary to further optimize the treatment of this rare vascular hepatic disorder.
Epithelial epithelioid hemangioendothelioma (HEHE) is a rare vascular tumor, which has an histologic appearance between hemangioma and hemangiosarcoma. Because of its rarity and highly variable evolution, the therapeutic algorithm of this disease is very debated and still far from standardized.

This analysis aims at a better definition of the value of liver transplantation (LT) in the current management of HEHE, based on a patient cohort of 59 patients reported to the European Liver Transplant Registry (ELTR).

PATIENTS AND METHODS

A detailed questionnaire, including 216 items, was sent to the 32 centers where 43 females and 16 males were transplanted for HEHE during the period June 1989 to June 2004. The first part of the questionnaire related to the pretransplant period including recipient data, biochemistry, clinical and radiologic presentation, disease-related complications, concomitant manifestations, extrahepatic disease localization, neo-adjuvant treatments, histologic examination, and quality of life. The second part focused on the peritransplant data including donor data, surgical aspects of transplant procedure, transfusion requirements, ischemia times, length of hospitalization, immuno-suppression (IS) and histologic examination of the native liver and lymph nodes (LN) including immunohistochemistry (IH).

The third part related to outcome, complications, incidence of rejection, biochemical and histologic follow-up, adjuvant treatment, current IS and quality of life after transplantation. Six (10%) questionnaires lacked 21 to 30 items and 11 (18.6%) more than 30 items. Lack of information was mainly because of the unavailability of several items related to the initially incorrect pretransplant diagnosis and to the insufficient knowledge of the disease presentation at the beginning of the studied time period. Definition of HEHE was based on the criteria established by Ishak, Weiss, and Dehner. Microscopically, HEHE is characterized by cells, both of medium and large size, which are epithelioid in appearance and that spread within sinusoids, terminal hepatic venules, and portal vein branches and often invade Glisson capsule. Intravenous growth may be in the form of a solid plug or polypoid or tuft-like projection. In contrast to hemangiosarcoma, the hepatic acinar landmarks (such as terminal hepatic venules and portal areas) are preserved.

Follow-up was complete for all patients with a median of 92.5 months (range, 7–369) from diagnosis and a median of 78.5 months (range, 1–245) from LT. All patients had a complete follow-up of minimal 5 years from the moment of diagnosis. Data are expressed as percentage, median values (range). Patient survival rates were calculated according to Kaplan–Meier; survival was calculated both from moment of diagnosis of HEHE and from moment of LT. Results are mostly given from moment of LT onwards. Early and late post-transplant events were determined as events occurring within or without the first 3 post-transplant months. Quality of life was evaluated using the Karnofsky score.

RESULTS

Median ages at moment of diagnosis and at moment of LT were 41 (range, 4–65) and 42 years (range, 4–65). Two patients were less than 15 years. The final diagnosis of HEHE was made in all patients by pathologic examination of the hepatectomy specimen. Fifty (84.7%) of 56 documented patients had pretransplant percutaneous (31 patients), surgical (18 patients), or percutaneous and surgical (8 patients) biopsies. Four biopsies were inconclusive; one percutaneous needle biopsy was followed by peritoneal seeding at the right diaphragm. Ten (16.9%) patients had extrahepatic disease localization in lung (5 patients), brain and bone (1 pt), peritoneum (1 pt), omentum (1 pt), femoral vein (1 pt), and spleen (1 pt). One patient each presented with cutaneous angiomata, vertebral angiomata and femoral enchondroma.

<table>
<thead>
<tr>
<th>TABLE 1. Biochemical Presentation of HEHE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter</td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td>AST</td>
</tr>
<tr>
<td>ALT</td>
</tr>
<tr>
<td>Tot Bil</td>
</tr>
<tr>
<td>Dir Bil</td>
</tr>
<tr>
<td>GGT</td>
</tr>
<tr>
<td>AP</td>
</tr>
<tr>
<td>Albumin</td>
</tr>
<tr>
<td>PT</td>
</tr>
<tr>
<td>Creatinine</td>
</tr>
<tr>
<td>Blood nitrogen</td>
</tr>
<tr>
<td>Haemoglobin</td>
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<tr>
<td>Platelet count</td>
</tr>
<tr>
<td>WBC</td>
</tr>
<tr>
<td>AFP</td>
</tr>
<tr>
<td>CEA</td>
</tr>
<tr>
<td>CA 19-9</td>
</tr>
</tbody>
</table>

*Percent of results in relation with collected information.
Clinical and biochemical presentation of HEHE in the 59 patients is shown in Tables 1 and 2. It should be noted that 11 (19%) patients were asymptomatic.

At time of LT, 47 patients were United Network for Organ Sharing status 4 (at home), 5 status 3 (regularly hospitalized), 6 status 2 (hospitalized), and 1 status 1 (intensive care bounded). Median Karnofsky scores at time of LT were 90 (range, 20–100).

Pretransplant radiologic investigation showed bilateral liver involvement in 47 (86%) of 56 documented patients. The liver lesions were isolated, confluent, and peripheral in 16 (32%), 26 (52%), and 8 (16%) of 50 documented patients. Portal and/or hepatic vein thrombosis or compression were seen in 10 of 20 (50%) and 13 of 24 (54%) documented patients. “Cocarde image,” capsula formation, and calcifications were present on imaging in 9 of 38 (24%), 11 of 44 (25%), and 6 of 47 (13%) documented patients, respectively.

Thirty-nine patients received tacrolimus and 29 cyclosporine, as part of quadruple, triple, or double immunosuppressive regimens with steroids and/or azathioprine (19 patients) and/or mofetil mycophenolate (4 patients) and/or rapamycin (2 patients). OKT3 and anti-IL2 receptor antibodies were used in 4 and in 2 patients, respectively.

Pretransplant Therapy and Interventions

Eighteen (30.5%) patients had pre-LT interventions. Seven patients had a previous liver resection; 1 patient each had a resection of a mediastinal tumor, a femoral vein, and a cerebral lesion. Liver surgery did not influence negatively the outcome of the LT procedure. Nine patients got adjuvant systemic or locoregional chemotherapy (CHTH) for their liver tumor. These treatments were based in all, but one, patient on a context of insufficient experience with the treatment of this liver disorder.

Peri- and Post-transplant Therapy and Interventions

Three patients presented at moment of LT an extrahepatic disease localization, 2 were pulmonary and 1 peritoneal. One patient underwent bilateral pulmonary resection for bilateral “solitary” lung lesion 29 months post-LT; she is doing well, disease free, 97 and 95 months postdiagnosis and post-LT. One patient had bilateral lung involvement; she underwent double lung transplantation followed by α-interferon treatment 21 months post-LT. She is doing well 69 and 65 months postdiagnosis and post-LT. One patient had simultaneous LT and diaphragmatic peritonectomy followed by systemic CHTH for peritoneal seeding due to percutaneous needle biopsy. He is doing well, disease free, 69 and 68 months postdiagnosis and post-LT. One patient underwent simultaneous LT and splenectomy; he recurred after 8 months and died 20 months post-LT.

From the 14 patients presenting recurrent disease, 7 received a therapy: radiotherapy (1×), combined radio-CHTH and radiofrequency destruction (1×), combined liver resection and CHTH (1×), combined pulmonary resection and CHTH (1×), resection of a breast lesion (1×), CHTH (1×), and hormonal therapy (tamoxifen) (1×) (Table 3).

Outcome After Transplantation

Classic LT was done in 27 patients, the other patients had a caval preserving implantation technique. Veno-venous bypass was used in 21 (35.6%) procedures (45.7%). Five and 3 patients were transplanted using split and living related LT techniques. Median operating time was 421 minutes (range, 185–1120). LT was technically rather easy as exemplified by low blood transfusion requirements (600 mL, range, 0–3300). Median intensive care and hospital stays were respectively, 3 (range, 1–20) and 19 days (range, 8–74). Pretransplant interventions technique of implantation and center experience did not have a negative impact on the transplantation procedure itself nor on outcome after LT.

One-, 5-, and 10-year patient survival rates of the whole patient cohort calculated from the moment of diagnosis are 97%, 83%, and 74%; the survival rates calculated from moment of LT are similar (93%, 83%, and 72%) (Fig. 1). One-, 5-, and 10-year patient post-transplant survival rates from moment of LT in relation to history of extrahepatic disease localization (n = 10), neo-adjuvant treatment (n = 18), LN invasion (n = 18), including 4 patients with positive F VIII positive LN HI at moment of LT and micro and macrovascular INV (n = 29) are displayed in Figures 1–4. The survival rates were only significantly different in the latter group. The difference in survival remains significant in case of microvascular invasion (Mi-INV) only (n = 24) (96%, 75%, and 52% vs. 96%, 92%, and 85%) in patients without Mi-INV (n = 30) (both P < 0.03).

Early (<3 months) mortality after LT was 1.7%; this patient died of massive liver necrosis due to hepatic artery thrombosis. Thirteen (22%) patients died during the late (≥3 months) post-LT period. Four patients died free of tumor...
RF, radiofrequency destruction; Mi/Ma, micro-/macrovascular invasion; RTH, radiotherapy.

Nine (90%), eight (82%), and six (64%) (Fig. 5). These survival rates are not significantly influenced by pre-LT carbohydrate early antigen (CEA) or alpha-fetoprotein elevation, pre-LT treatment, LN status, extrahepatic disease localization, and vascular invasion.

Eleven (18.6%) patients had complications related to the transplant procedure. The surgical complications were as follows: primary nonfunction (1 patient), small for size syndrome (1 patient), hepatic artery thrombosis (5 patients), intraabdominal bleeding (1 patient), and biliary complication (8 patients). Twenty-five (42.3%) patients had medical complications: renal (5 patients) and respiratory (4 patients) failure; cholangitis (3 patients), severe bacterial (12 patients), viral (10 patients), and fungal (4 patients) infections.

Acute rejection occurred in 10 (17%) patients. In all, but one, case it occurred during the first month. Two rejection episodes were corticosteroid-sensitive, 4 required OKT3 or antithymocyte globulin therapy, and 4 patients were switched to antithymocyte globulin therapy, and 4 patients were switched to antithymocyte globulin therapy.

### TABLE 3. Mortality and Recurrent Disease After Liver Transplantation for HEHE

<table>
<thead>
<tr>
<th>Patients</th>
<th>Pre-LT Imaging</th>
<th>Age at LT</th>
<th>LN/Micro- Macro-vascular Invasion</th>
<th>Site</th>
<th>Time between LT-recurrence</th>
<th>R/</th>
<th>Alive</th>
<th>Death Time from Diagnosis/LT Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Multiple</td>
<td>69</td>
<td>-/+/-</td>
<td>Skin, lung</td>
<td>8</td>
<td>N</td>
<td>111/8 mo multiorgan failure, sepsis</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Multiple, confluent, bilateral, HV compression</td>
<td>42</td>
<td>-/+/-</td>
<td>Abdomen</td>
<td>18</td>
<td>N</td>
<td>30/27 mo de novo lung cancer</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>Multiple, isolated, bilateral, Hepatic-Portal compression</td>
<td>40</td>
<td>-/+/-</td>
<td>Bone</td>
<td>10</td>
<td>RTH</td>
<td>8/1 mo, necrosis following HAT</td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>Multifocal, confluent</td>
<td>30</td>
<td>-/+/-</td>
<td>Liver, lung bilateral</td>
<td>58</td>
<td>Liver resection-CHTH</td>
<td>73/70 mo de novo lung tumor</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>Multiple, bilateral, confluent</td>
<td>47</td>
<td>-/+/-</td>
<td>Liver</td>
<td>73</td>
<td>N</td>
<td>32/21, PNF after ReLT for HAT biliary sepsis</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Multiple, bilateral, HV compression; Spleen</td>
<td>65</td>
<td>-/+/-</td>
<td>Skin, lung</td>
<td>8</td>
<td>N</td>
<td>30/23 mo REC</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Multiple, bilateral, isolated</td>
<td>38</td>
<td>-/+/-</td>
<td>Abdomen</td>
<td>18</td>
<td>N</td>
<td>24/24 mo REC</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Multiple, bilateral</td>
<td>42</td>
<td>-/+/-</td>
<td>Bone</td>
<td>10</td>
<td>RTH</td>
<td>13/13 mo REC</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>Multiple, isolated, bilateral</td>
<td>48</td>
<td>-/+/-</td>
<td>Liver, lung bilateral</td>
<td>58</td>
<td>Liver resection-CHTH</td>
<td>84/73 mo REC</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>Multiple, bilateral</td>
<td>52</td>
<td>+/-/+</td>
<td>Liver</td>
<td>15</td>
<td>N</td>
<td>21/15 mo REC</td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>Multiple, bilateral</td>
<td>30</td>
<td>-/+/-</td>
<td>Lung</td>
<td>40</td>
<td>N</td>
<td>46/41 mo REC</td>
<td></td>
</tr>
<tr>
<td>44</td>
<td>Multiple, bilateral</td>
<td>54</td>
<td>-/+/-</td>
<td>Liver</td>
<td>73</td>
<td>N</td>
<td>163/79 mo REC and Burkitt’s lymphoma</td>
<td></td>
</tr>
<tr>
<td>57</td>
<td>Multiple, bilateral, confluent; omentum</td>
<td>35</td>
<td>+/+/+</td>
<td>Liver</td>
<td>N</td>
<td>N</td>
<td>10/9 mo REC</td>
<td></td>
</tr>
<tr>
<td>58</td>
<td>Multiple, bilateral, confluent, with omental and duodenal LN (palliative LT due to pain)</td>
<td>31</td>
<td>+/+/+</td>
<td>Bone marrow, spleen, Liver</td>
<td>3</td>
<td>CHTH (tamoxifen)</td>
<td>16/3 mo REC</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Right lobe, peripheral</td>
<td>47</td>
<td>+/+/-</td>
<td>Liver</td>
<td>80</td>
<td>RTH-CHTH-RF</td>
<td>152/112 mo AWD</td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>Eight isolated nodules, bilateral</td>
<td>64</td>
<td>+/+/-</td>
<td>Lung</td>
<td>9</td>
<td>Lung resection, CHTH</td>
<td>85/84 mo AWD</td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>Multiple, isolated, bilateral + thoracic</td>
<td>38</td>
<td>-/+/-</td>
<td>Liver, skin</td>
<td>98</td>
<td>N</td>
<td>369/211 mo AWD</td>
<td></td>
</tr>
<tr>
<td>33</td>
<td>Multiple, bilateral, PV compression + pulmonary AV fistula</td>
<td>43</td>
<td>-/+/-</td>
<td>Liver, breast</td>
<td>84/156</td>
<td>Resection breast lesion</td>
<td>224/212 mo AWD</td>
<td></td>
</tr>
<tr>
<td>56</td>
<td>Five nodules, right lobe, isolated</td>
<td>52</td>
<td>-/+/-</td>
<td>Lung</td>
<td>18</td>
<td>CHTH</td>
<td>68/59 mo AWD</td>
<td></td>
</tr>
</tbody>
</table>

AWD indicates alive with disease; NA, not available; CHTH, chemotherapy; PNF, primary-nonfunction; HAT, hepatic artery thrombosis; REC, recurrence; LN, lymph node; RF, radiofrequency destruction; Mi/Ma, micro-/macrovascular invasion; RTH, radiotherapy.
from cyclosporine to tacrolimus. Chronic rejection was diagnosed once after late steroid withdrawal.

Median Karnofsky score improved in 46 long-term survivors from 90 (range, 20–100) pre-LT to 100 post-LT (range, 80–100).

**Histologic Examination of the Hepatectomy Specimen**

Median weight of the hepatectomy specimen was 1250 g (range, 700–1113). Gross macroscopic appearance of HEHE was nodular in 74% (40 of 54 patients) and diffuse in 26% (14 of 54 patients). HEHE was always a multinodular (86% of patients had more than 15 lesions) and nearly always a bilobar in 96% (50 of 54 patients) disease. Three patients presented pseudo-cirrhosis due to hepatic remodeling induced by the vascular disease process. Macrovascular and microvascular INV was present in 9.4% (5 of 53 patients) and 44.4% (24 of 54 patients) of patients. IH of liver tissue was positive for F VIII in 91% (39 of 43) of documented patients. Hilar LN were invaded in 18 of 54 (33.3%) patients; in 4 of them, invasion could be demonstrated by IH only. In 3 of 52 (5.7%) patients, there were suspected foci of hemangiosarcoma; they are alive disease-free at 157 and 173 and with disease recurrence at 103 months post-LT.

**DISCUSSION**

HEHE is a rare, low-grade malignancy, which has a highly variable evolution. It is a soft tissue vascular tumor with an estimated incidence of less than 1 per million people. This tumor was first recognized in soft tissues, then in the head and neck region, bones, and later on in many other organs such as spleen, stomach, breast, heart, penis, thyroid, peritoneum, and lungs. Weiss and Enzinger recognized the similarity between HE and the intravascular...
bronchio-alveolar tumor described in 1975 by Dail et al.\textsuperscript{14} Liver involvement occurs most often as a primary tumor.\textsuperscript{1,6,16,17} Ishak was the first to report, in 1984, the features of HEHE in a series of 32 patients.\textsuperscript{1} HEHE is more frequent in adult women (gender relation male/female 2/3). HEHE can occur at any age although the tumor is exceptionally reported in children younger than 15 years.\textsuperscript{1,2,4,15,18} Although different etiologic factors (eg, oral contraceptives and exposure to polymeric materials) were suspected, there is no definitive etiological factor that has been clearly identified for HEHE.\textsuperscript{1,2,4–6,12,17,19}

HEHE is a vascular tumor, which is intermediate between hemangioma and hemangiosarcoma.\textsuperscript{1,6} The definition of HEHE, as a unique form of vascular lesion whose origin are the endothelial cells, is based on IH positive staining for factor VIII-related antigen, and for CD31 and 34 endothelial markers in the tumor, and on specific ultrastructural findings.\textsuperscript{1,4–7,17,18,20}

The clinical manifestation of HEHE is unspecific and variable, going from an asymptomatic state to hepatic failure. The disease course is a protracted, relatively benign one; the longstanding clinical history and the presence of intratumoral calcification can be of help to make the diagnosis.\textsuperscript{1,2,4,16,17,20,27} The final diagnosis can only be made by IH and ultrastructural examination of appropriate material obtained from adequate surgical or guided needle biopsy specimens.\textsuperscript{1,4,16–18}

HEHE should be differentiated from hematinfantile HE (HIHE). Both have different age-related, clinical, and pathologic features.\textsuperscript{1,5,6,8,28–30} HIHE, the most common tumor of the liver in the infant age (<3 years) group, is nearly always diagnosed during the first 6 months of life. HIHE is also more frequent in females and presents with a symptomatic hepatosplenomegaly, failure to thrive, congestive cardiac failure (15%) due to intratumoral arteriovenous shunting and cutaneous hemangiomas (20%–40%). HIHE seems to be a histologic benign tumor, which may have a poor outcome because of its complications such as heart failure.\textsuperscript{3,29} The differentiation between HEHE and HIHE (which can be seen exceptionally in adults) is important because the latter does not metastasize. Several lesions, present simultaneously in different organs such as spleen, lungs and bone, should be seen as separate lesions.\textsuperscript{29} Treatment modalities of HIHE go from medical (antiangiogenic) therapies to interventional radiology and partial or total liver resection.\textsuperscript{3,7,8}

The treatment algorithm of HEHE is far from standardized mainly due to its rarity and the inability to predict its behavior and therefore the prognosis. The literature review learns that there are only 12 papers including “series” of 5 (to maximal 16) cases\textsuperscript{1,6,18,23,31–41} and 3 reviews compiling data about 127,137, and 434 patients.\textsuperscript{2,4,5} These small series and larger reviews however include same patients, are heterogeneous and lack detailed data analysis about pre and post-treatment period, treatment modalities, histology, and (long-term) follow-up. The number of patients having had partial or total hepatectomy, which is a prerequisite to obtain a good idea about disease staging and aggressiveness, is moreover reduced in the 3 aforementioned reviews to 36 (of 124); 13 (of 137) and 128 (of 434) patients respectively. The published experience does not allow to compare results of untreated and of surgically and medically treated patients and also raises greater vessels and cause a nodular transformation of the uninvolved liver. Focal calcifications are found in 20% of tumors. The internal architecture of the tumors is best depicted on T2-weighted magnetic resonance imaging.\textsuperscript{2,4,20,24} Angiography reveals only moderate vascularization with displacement of marginal vessels.\textsuperscript{2,23,24} Scintigraphic and fluorodeoxyglucose-positron emission tomography imaging may have an important role in the staging of EHE, especially in view of later LT.\textsuperscript{25,26}

Because of its aspecific evolution, rarity, and pleomorphism of the tumor cells, diagnosis may be difficult and misdiagnoses (ranging from giant hemangioma to unclassified sarcoma) are frequent.\textsuperscript{1,2,4–6,16} F VIII immunostaining should, therefore, be done in all sclerotic and calcified as well as in all liver tumors of unclear origin. The association of radiologic features with a peculiar set of clinical findings such as the occurrence in a young adult, the contrast between numerous intrahepatic tumors and the good condition of the patient; the longstanding clinical history and the presence of intratumoral calcification can be of help to make the diagnosis.\textsuperscript{1,2,4,16,17,20,27} The final diagnosis can only be made by IH and ultrastructural examination of appropriate material obtained from adequate surgical or guided needle biopsy specimens.\textsuperscript{1,4,16–18}

\textbf{FIGURE 5.} Recurrence free actuarial patient survival from moment of LT.
controversy about indication for LT.\textsuperscript{2,16} The place of LT in the treatment of HEHE is particularly questioned in view of (a) the well documented spontaneous, long-term survivals (up to 28 years),\textsuperscript{1,2,4,8} (b) the 28\% to 45\% reported incidence of extrahepatic, mostly pulmonary, osseous, peritoneal and/or LN, disease,\textsuperscript{1,2,4,7} (c) the lack of clinical or histologic criteria to predict the evolution of the disease,\textsuperscript{1,4,7,23,31,32} and (d) the 24\% (these series) to 33\% reported incidence of recurrent allograft disease.\textsuperscript{31,32,36,42}

The Pittsburgh (16 patients) and the Cincinnati Cancer Transplant Registry (25 patients) series showed that LT offers good survival, the 5-year actuarial patient and disease-free survival rates after LT being 71\% to 67\% and 60\% to 43\%, respectively.\textsuperscript{32,33,35} The Mehrabi review indicates that the treatment of choice of HEHE is total hepatic resection.\textsuperscript{5} In this review, 1- and 5-year survival rates of LT [applied in 44.8\% of (reported) patients], partial liver resection (applied in 9.4\% of patients), local or systemic chemo- and radiotherapy (applied in 21\% of patients) and treatment abstention (applied in 24.8\%) were 96\% and 55\%, 100\% and 75\%, 73\% and 30\%, 39\% and 0\%, respectively. Partial resection is not a good treatment because HEHE is often a multinodular and bilobar disease and the tumor behaves aggressively after partial liver resection, a feature explained by the fact that the liver regeneration depends on angiogenesis.\textsuperscript{2,34} The assessment of nonsurgical treatments such as radiotherapy, local treatments such as tumor alcoolisation and radiofrequency destruction, hemonotherapy, systemic or locoregional CHTH, arterial embolization, and chemoembolization is even more difficult because of the scarcity of (prospective) data collection, the lack of uniform treatment modalities and of detailed long-term follow-up.\textsuperscript{4,5} Different medical treatments such as \textalpha-interferon, thalidomide, and vincristine have been reported to influence the disease course.\textsuperscript{43–47} These treatments may become of value as (neo)adjuvant therapies in the setting of LT.\textsuperscript{2,4–6,16}

This, largest ever reported, multicenter study, is of particular interest as it contains a detailed and complete long-term follow-up (from minimal 5–30 years from moment of diagnosis) of 59 European HEHE transplant recipients. The study validates the place of LT in the treatment of HEHE as the 5- and 10-year post-LT survival rates are 83\% and 74\%, numbers largely superior to those reported till now. This study also brings some light in the till now unclear correlation between histologic and clinical staging and outcome.\textsuperscript{2,5,6,20,31,34} The study confirms previous isolated findings that invasion of LN and presence of (limited) extrahepatic disease involvement are indeed no formal contraindications to LT.\textsuperscript{16,23,31,34,44} Histology of the hepatectomy specimen confirmed that vascular invasion significantly influences outcome after LT. The mitotic index, presence of necrotic and fibrotic cellular areas and cellular pleomorphism, supposed to be possible histologic prognostic criteria reflecting biologic aggression, of the tumor, could not be analyzed in this study.\textsuperscript{1,2,4,25,31} The different findings of the study are in favor for proposing LT earlier in the disease course of, even asymptomatic, HEHE.

The real value of LT in the treatment of HEHE can only be measured by analyzing disease-free survival rates beyond 5 and, even better, 10 years as very long spontaneous survival after diagnosis and 5-year survivals have been repeatedly reported after surgical (partial or total), even incomplete, resection, even in presence of extrahepatic disease localizations and as allograft or extrahepatic disease recurrence or manifestation can been seen many years (in Penn’s series mostly after 2 years; in these series from 6 to 79 months) post-LT,\textsuperscript{1,2,4,5,16,23,33,34,48} Recurrent disease should be treated aggressively as prolonged (up to 10 years in these series), sometimes even disease-free survival can be obtained.\textsuperscript{35} The role of retransplantation in the treatment of recurrent allograft disease remains open as only 1 case has been published so far without beneficial result.\textsuperscript{20} In view of the results observed in some patients in these series presenting recurrent disease this policy merits a reevaluation. The same reflection holds for the treatment of extrahepatic recurrent disease. The high incidence of HEHE recurrence, in- and outside the allograft, should lead to the introduction of LT and antiangiogenic, neo- and adjuvant, combination therapies using anti-vascular endothelial growth factor (V-EGF)-antibodies and the novel immunosuppressant rapamycine. Better tumor staging by more deliberate use of scintigraphy, laparo- and thoracoscopy (with adequate tissue sampling) and IH examination of LN procured at moment of (staging) surgery as well as determining the biologic behavior of the tumor, based on molecular markers, will be of help to improve outcome of HEHE patients. Analyzing the expression of genes such as V-EGF, TP53 murine double minute-2, caveolin-1, known to be involved in the pathogenesis of vascular tumors, may be helpful not only for determination of biologic behavior but also for monitoring the efficacy of emerging neo- and adjuvant treatments.\textsuperscript{36,50} Such measures would allow to recognize patients having aggressive subtypes of HEHE and to explain rapid and aggressive disease recurrence.

CONCLUSION

This ELTR-ELITE survey is the first large study with long-term follow-up, to focus on the value of LT in the treatment of this rare vascular hepatic disorder. In view of the obtained results, a more aggressive attitude toward HEHE seems to be warranted after a thorough staging of the disease has been performed. This attitude remains valid even in the presence of close (LNs) or distant extrahepatic disease localization. The prognosis of this disease might be improved in a near future by combining radical surgery and targeted (neo-)adjuvant antiangiogenic CHTH. A systematic registration of all vascular liver tumors with prospective and long-term data collection, will be the best way to further improve the outcome of HEHE patients.
REFERENCES


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Discussions

Professor K. Hockerstedt: You are to be congratulated not only for the largest study in the world, but also for one with the longest follow-up. I will concentrate on the diagnosis because that affects the results and your conclusions. I read your manuscript but I am still unclear about the histologies of the patients. Do you have the exact histologies and were there any common features?

Also, you say that, in the lymph nodes in 4 patients, only the immune histochemistry of the F-8 revealed some metastases. My question is: you had histology for most of the lymph nodes but did you have immunohistochemistry for F-8 for all of them?

My final question relates to the fact that F-8 is not diagnostic for this tumor. You find it in hemangioma and in angiosarcoma, and it only shows that it is a vascular tumor. So, did you have any possibility of obtaining results from CD31 or any of the other markers?

Professor J. Lerut: The issue of histology is, of course, important. We had the complete histologic report for all the patients. The differentiation in this disease is found in the infantile form of the disease, which sometimes exists in adults and, of course, with hemangiosarcoma. The difference is very simple for the pathologist; in the hemangioendothelioma the acinar landmarks of the liver structure such as hepatic venules and portal areas are preserved whereas they are destroyed in angiosarcoma.

Professor K. Hockerstedt: But did you have that report from all patients?

Professor J. Lerut: I think we had them from all 59 patients. It is the same for the lymph nodes. The immunohistochemistry on the lymph nodes was however not done in all patients. We just looked at the supplementary information regarding lymph node status obtained in some of the patients. Immunohistochemistry was done in about half of the patients. It would have been optimal to have at our disposal all slides read by a single central pathologist, but this was impossible to obtain.

Professor H. Bismuth: Do you recommend liver transplantation for all cases? Do you want to exclude those with micro and macrovascular invasion? And in this case, how do you know that before?

Professor J. Lerut: In my opinion, you should transplant them all because you cannot know the microvascular invasion. It is similar to hepatocellular cancer except here you do not have a similar tumor.
Localized Hepatic Ischemia After Liver Resection

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Objective: To prospectively assess the frequency, severity, and extension of localized ischemia in the remaining liver parenchyma after hepatectomy.

Background: Major blood loss and postoperative ischemia of the remnant liver are known factors contributing to morbidity after liver surgery. The segmental anatomy of the liver and the techniques of selective hilar or suprahilar clamping of the Glissonian sheaths permit identification of ischemia on the surface of the corresponding segments for precise section of the parenchyma. Incomplete resection of a segment, or compromised blood supply to the remaining liver, may result in ischemia of various extension and severity.

Methods: Patients undergoing hepatectomy received enhanced computerized tomodensitometry with study of the arterial and venous phases within 48 hours after resection. We defined hepatic ischemia as reduced or absent contrast enhancement during the venous phase. We classified the severity of ischemia as hypoperfusion, nonperfusion, or necrosis. The extension of ischemia was identified as marginal, partial, or segmental. Factors that may influence postoperative ischemia were analyzed by univariate and multivariate analyses.

Results: One hundred fifty consecutive patients (70 F, 80 M, mean age 62 ± 12 years) underwent 64 major and 81 minor hepatectomies and 5 wedge resections. We observed radiologic signs of ischemia in 38 patients (25.3%): 33 hypoperfusions (17 marginal, 12 partial, and 4 segmental), 3 nonperfusions (1 marginal, 1 partial, and 1 segmental), and 2 necroses (1 partial, 1 segmental). One patient with a segmental necrosis underwent an early reoperation. In all other cases, the evolution was spontaneously favorable. Postoperative peak levels of serum aspartate aminotransferase and alanine aminotransferase were significantly higher in patients with ischemia. Patients with ischemia had a significantly higher risk of developing a biliary leak (18.4% vs. 2.6%, *P* < 0.001). There was no correlation between liver ischemia and mortality (2%). None of the following factors were associated with ischemia after univariate and multivariate analysis: age, preoperative bilirubin level, liver fibrosis, malignant tumor, type of hepatectomy, surface of transection, weight of resected liver, Pringle maneuver, blood loss, and number of transfusions.

Conclusions: Some form of localized ischemia after hepatectomy was detected in 1 of 4 of our patients. Its clinical expression was discreet in the large majority of cases, even if it might have been one of the underlying causes of postoperative biliary fistulas. Clinical observation is sufficient to detect the rare patient with suspected postoperative liver ischemia that will require active treatment.


Understanding of the segmental anatomy of the liver has made it possible to perform various types of hepatectomies, the removal of single segments or groups of segments of the liver, thereby adapting the extent of parenchymal resection to the clinical situation of the specific patient.1,2 The blood supply to the liver parenchyma relies on the intrahepatic distribution of the portal pedicles, therefore complete resection of the territory depending of the interrupted vessels is necessary to avoid leaving residual ischemic parenchyma after liver resection. Accidental damage to an inflow vessel of an adjacent segment can result in liver ischemia to the vascular distribution area of the damaged vessel. Leaving ischemic parenchyma after hepatectomy, either because of insufficient or excessive resection, represents a risk even when based on the intrahepatic distribution of portal pedicles and liver segmentation.

A number of publications have focused on ischemic damage of the liver after hepatectomy. These studies have mainly addressed the consequences of intraoperative complete or partial temporary hepatic blood inflow occlusion and ischemic reperfusion injury on the remaining parenchyma.3,4 Information on localized ischemic damage to the liver after hepatectomy is limited. The aim of our study was to assess the frequency, severity, and extension of focal ischemia of the liver after hepatectomy and to analyze the possible causes and consequences of this complication.

PATIENTS AND METHODS

All patients submitting to hepatectomy between 1996 and 2006 were prospectively studied. The following patient information was recorded: demographic data, indications for surgery, preoperative bilirubin level, presence of liver fibro-
sis, type of operation performed, postoperative peak level of serum aspartate aminotransferase and alanine aminotransferase or presence of biliary leakage, and 30-day mortality. Biliary leakage was defined as drainage of bile persisting over 4 days, regardless of the volume drained though the suction drains, or as intra-abdominal fluid collection containing bile at percutaneous aspiration and drainage. All patients underwent enhanced computed tomodensitometry (CT) within 48 hours after surgery.

Hepatectomy Technique and Definitions

The nomenclature of hepatectomies is based on liver segmental anatomy as described by Couinaud and on the Brisbane 2000 system. Hepatectomy extension was defined as major (more than 2 segments) or minor. Hepatectomy type was defined as standard or segmental. Standard resections consisted of right or left hepatectomies, extended right hepatectomy or left lateral sectionectomy. The preoperative resection plan was based on 2-dimensional CT imaging of the liver. All hepatectomies were performed under general anesthesia with controlled central venous hypotension through subcostal incision with upper midline extension. The liver was mobilized according to the type of resection that was planned preoperatively. The lesions to be resected were identified by bimanual palpation and intraoperative ultrasonography. The ultrasonography was also used to screen the liver for other lesions and to identify the intrahepatic anatomy. In right or left hepatectomies, the hilar plate was lowered and the elements of the ipsilateral portal pedicle were individually dissected, transected, and sutured. “En masse” ligature was not used in these instances. In resections involving sections of portal triads of second or third order, at distance of the hilus, the portal triads to the segments or groups of segments to be resected were, whenever possible, encircled with rubber tapes for selective clamping and subsequent en masse ligature. The limits of resection on the surface of the liver were defined by ischemic demarcation after selective clamping or by external and internal ultrasonographic anatomic landmarks. Wedge resections were guided only by the location of the lesion being excised, irrespective of other criteria.

Parenchymal transection was performed using a crushing clamp or an ultrasonically activated blade. The larger intrahepatic structures encountered were ligated or coagulated before transection. Intermittent Pringle maneuver was used only when parenchymal transection bleeding was in excess of 200 mL (15 minute clamping periods separated by 5 minute intervals). After hepatectomy, saline was injected through the cystic duct to detect biliary leakage on the cut surface of the liver and on biliary stumps. Identified leakages were repaired with fine polydoxanone sutures. In all cases, the abdominal wall was closed over a suction drain lying close to the cut surface of the liver.

After resection, the cut surface of the liver was reproduced and measured on millimetric paper and the weight of the resected liver was recorded. The blood loss volume, the number of red blood cell (RBC) packs transfused, and the use of the Pringle maneuver were also recorded.

Imaging Technique and Definitions

From 1996 to 2003 the data collected consisted of contrast-enhanced CT images that were obtained with a single detector spiral scanner (Philips Tomoscan AV-1). From 2004 to 2006 images were obtained with a multidetector Philips Brilliance CT 16 scanner (Philips Medical Eindhoven, the Netherlands). From 1996 to 2003 images were obtained with a table speed of 5 mm/s, a layer thickness of 5 mm (pitch 1:1), and a slice increment of 3 mm (corresponding to 2 mm overlapping). From 2004 on, the slice thickness was 2 or 3 mm and the collimation was 1.5 mm with reconstructed slices every 2 mm. The vascular contrast was optimized using a bolus tracking procedure (120 mL of Optiray 350, application speed 4 mL/s; Guerbet Laboratories Paris, France) for the arterial and venous phases with study the late parenchymal phase.

Images of all CT phases (avascular, arterial, portal, late) were analyzed by a radiologist and a surgeon. The usual radiologic criteria for assessment of liver hypovascularization and necrosis on CT were adopted. Ischemia was defined as reduced or absent contrast enhancement during the portal phase with a severity of hypoperfusion, nonperfusion, or necrosis. Hypoperfusion was characterized by the diminution of contrast enhancement in the liver parenchyma and the presence of contrast enhancement in the intrahepatic vessels. Nonperfusion was a complete absence of parenchymal and vascular contrast enhancement. Necrosis included all the criteria of nonperfusion in addition to the presence of air in the liver tissue. The extension of ischemia was defined as segmental (involving an entire hepatic segment), partial (in-

![FIGURE 1. Marginal hypoperfusion. The limit of the zone of ischemia (marked with arrows) is close to the resection margin. Hypoperfusion is characterized by reduced contrast enhancement with intrahepatic contrast-filled vessels during portal phase.](image_url)
volving part of a segment), or marginal (ischemia limited to the resection margin) (Figs. 1–3).

Repeated postoperative images from successive CT scans showed the evolution of the ischemic lesions. Outcome was described as full recovery, atrophy, or disappearance of the ischemic liver territory.

Analysis and Statistics

The postoperative evolution of patients with and without localized ischemia was compared. Univariate and multivariate analysis was performed to determine whether localized ischemia was correlated with preoperative or operative factors. Results were expressed as the mean with standard deviation and as the median with range when appropriate. Quantitative variables were analyzed with a Student t test and qualitative variables with a χ² test. Univariate odds ratios with 95% confidence intervals were calculated. Results were then introduced in a multivariate logistic regression model. Statistical significance was set at P < 0.05. The data were analyzed with JMP IN software, version 5.1 (SAS institute Inc.).

RESULTS

One hundred fifty patients (70 F, 80 M) with a mean age of 62 ± 12 years were treated for 26 benign and 124 malignant conditions. The main indications for surgery were colorectal metastases or hepatocarcinomas, among other pathologies (Table 1). We performed 64 major and 86 minor hepatectomies, including 5 wedge resections; 76 operations were characterized as standard hepatectomies (Table 2). Liver fibrosis was present in 47 patients (31.3%) and in 12 patients the preoperative bilirubin level was higher than 34 μmol/L (normal level <17 μmol/L).

The Pringle maneuver was used in 76 patients (51%). Blood loss ranged from 100 to 6000 mL (median 450 mL; mean 771 ± 867 mL) and 43 patients (28.7%) received between 2 and 9 packed RBCs (median 2; mean 3.16 ± 1.82 packed RBCs). The mean cut surface of the liver was 83 ± 53cm² and the mean weight of the resected liver 462.5 ± 460 g.

Ten biliary leakages were all revealed by the suction drain left in place during the operation. Resolution was spontaneous in all cases, but the hospital stay was significantly longer when compared with the other 140 patients (main stay 21.3± 10.9 days vs. 15 ± 6 days, P < 0.05). The 30-day mortality was 2%.

We observed radiologic signs of ischemia in 38 patients (25.3%): 33 hypoperfusions, 3 nonperfusions, and 2 necroses. In 37 patients, localized ischemia had no clinical expression. The local extension of ischemia (marginal, partial, segmental) and its evolution are given in Table 3. Hypoperfusion evolved into complete radiologic resolution. This spontaneous recovery was indicated by the normal appearance of the liver in repeated contrast enhanced CT scan. Nonperfusion ischemia evolved into liquefaction. Two patients had ischemic necrosis. In one, resection of segment VI for hepatocellular carcinoma caused segment VII necrosis. The patient developed fever, tachycardia, pain, and leukocytosis 30 hours after surgery (Fig. 3). The necrotic segment was resected on the third postoperative day and the evolution was then uncomplicated. The other patient with partial necrosis presented with an unremarkable clinical evolution after prophylactic antibiotic therapy and conservative treatment of a biliary

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**TABLE 1. Indications for Hepatectomies**

<table>
<thead>
<tr>
<th>Indications</th>
<th>No. Hepatectomies</th>
</tr>
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<tbody>
<tr>
<td>Colorectal metastases</td>
<td>51</td>
</tr>
<tr>
<td>Hepatocarcinoma</td>
<td>47</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>19</td>
</tr>
<tr>
<td>Metastases from other origins</td>
<td>7</td>
</tr>
<tr>
<td>Benign pathologies</td>
<td>26</td>
</tr>
</tbody>
</table>
leakage. The ischemic territory vanished in subsequent radiologic scans.

A comparison of patients with and without radiologic signs of ischemia is shown in Table 4. Patients with ischemia had a higher postoperative peak level of serum aspartate aminotransferase and alanine aminotransferase ($P < 0.001$) and more biliary leaks ($18\%$ vs. $2.6\%, P < 0.001$). There was no correlation between liver ischemia and postoperative mortality.

The factors introduced in the univariate and in the multivariate analysis are shown in Table 5. None of these factors were significantly associated with ischemia in the multivariate analysis.

**DISCUSSION**

Interrupting vascular inflow to the pathologic liver before transection of the parenchyma results in ischemia in the dependent territory. The visible discoloration on the surface of the liver showing the line of ischemic demarcation, along with the external and internal hepatic landmarks, indicates the plane of section to be followed by the surgeon. Corrosion casts, and more recently imaging, have demonstrated that the limits between the different liver segments are far from constant and do not correspond to flat planes but adopt various curved shapes. It is therefore likely that in many hepatectomies, although performed according to the segmental anatomy of the liver, the transection planes do not correspond exactly to the intersegmental limits. As a consequence, parenchyma affiliated with devascularized segments will remain unresected, and parenchyma affiliated with nearby vascularized segments will be unnecessarily resected. The latter implies a risk of lesion to vascular and biliary structures in the unresected segment. The close vicinity of the arterial and portal branches and of the bile duct within the Glissonian sheaths suggests a risk of simultaneous lesion to these structures resulting in ischemia and biliary leakage, this risk increasing as the surface of the cut section is extended. Yet surprisingly, the cut surface and the weight of the resected liver were not related to postoperative liver ischemia in our univariate analysis.

The risk of cutting the liver in an inexact plane may seem less relevant in standard than in segmental hepatectomies. In the former, a single transection plane follows easily detectable anatomic or ischemic landmarks. In the latter, intersegmental boundaries are more difficult to identify, and often more than 1 transection plane is necessary to detach single or multiple segments from the rest of the liver. Yet, in our univariate analysis, localized ischemia was only mildly associated with the type of hepatectomy ($P = 0.06$) and a statistically significant association was absent. Neither was localized ischemia associated with the extent of hepatectomy defined as major or minor.

In addition to the vascular structures of the portal triads, branches of the hepatic veins may also suffer injury during hepatectomies. The resulting congestion of the liver parenchyma could translate into typical perfusion abnormalities detectable on CT scans. Hepatic vein occlusion involving single segments, with localized intrahepatic venous con-

| TABLE 2. Characteristics and Number of Hepatectomies |
|---------------------------------|-----------------|-----------------|-----------------|
| Type of Hepatectomy             | Resected Segments | Total Number   | Without Ischemia | With Ischemia   |
| Major hepatectomies             |                  |                |                 |               |
| Right hepatectomy*              | V-VI-VII-VIII    | 35             | 28              | 7              |
| Left hepatectomy*               | II-III-IV        | 8              | 4               | 4              |
| Extended right hepatectomy*     | IV-VI-VII-VIII   | 8              | 7               | 1              |
| Extended left hepatectomy*      | I-II-III-I-V-VII | 3              | 2               | 1              |
| Three segments                  | IV-V-VII/II-III  | 10             | 6               | 4              |
| Minor hepatectomies             |                  |                |                 |               |
| Left lateral sectionectomy*     | II-III           | 25             | 23              | 2              |
| Other bisegmentectomies         | VI-VII/IV-V-VII  | 30             | 20              | 10             |
| Monosegmentectomy               | All except segment II | 26          | 17              | 9              |
| Wedge resection                 | —                | 5              | 5               | 0              |

*Standard hepatectomies.

| TABLE 3. Radiological Evolution and Treatment of Localized Ischemic Lesions |
|---------------------------------|-----------------|-----------------|
| Severity                        | Extension       | Radiological Evolution | Treatment |
| Hypoperfusion                   | 17 marginal     | Complete recovery | ttt leak (n = 2) |
|                                 | (n = 17)        | (n = 12)         | |
| Nonperfusion                    | 1 marginal     | Liquefaction and vanishing of liver tissue | — |
|                                 | (n = 4)        | (n = 4)         | |
| Necrosis                        | 1 marginal     | Vanishing of liver tissue | tt leak |
|                                 | 1 partial      | (n = 4)         | |
|                                 | 1 segmental    | (n = 4)         | |
|                                 | Segment resected | Segment resection | |

n indicates number of patients; ttt leak, conservative treatment of biliary leakage.
gestion, has been shown to produce a confusing radiologic image mimicking inflow insufficiency.\textsuperscript{21,22}

The most severe form of ischemia, nonperfusion and necrosis, as observed in 5 patients, had a similar evolution suggestive of liver infarction. Although it seems likely that liver infarction was caused by interruption of the vascular inflow at the base of the segment, the instances of less extensive and severe ischemia could have had various causes. The most likely would be remnants of nonvascularized liver tissue as a consequence of differences between the plane of surgical transection and the real segmental boundaries, or localized interruption of the hepatic venous return by transection of a branch of a hepatic vein.

It may be surprising that some form of localized ischemia was observed after only 25% of hepatectomies, given the fact that the suspected operative causes of ischemia are likely to occur with great frequency. An explanation for this may be that the vascular system of the liver has a remarkable ability to adapt to vascular occlusions. A tolerance to interruption of either the arterial or the portal hepatic blood flow has been recognized for years.\textsuperscript{23–25} Compromise of the hepatic venous drainage system also results in local intrahepatic adaptation, through development of collateral circulation and directional changes of flow in the portal branches.\textsuperscript{26}

One can therefore assume that the vascular lesions that occur during hepatectomies remain largely undetected because of the various mechanisms safeguarding the parenchymal vascularization. These mechanisms are most efficacious when hepatocytes are capable of increasing the oxygen extraction from the limited blood supply. Shock, hypoxia, sepsis, or cholestasis increase the vulnerability of liver cells and increase the risk of necrosis.\textsuperscript{27,28} Shock and jaundice were not identified as promoting ischemia in our univariate and multivariate analysis. Indeed, neither blood loss nor the

\begin{table}[h]
\centering
\begin{tabular}{l|c|c|c|c}
\hline
\textbf{Characteristics} & \textbf{All Patients} & \textbf{No Ischemia} & \textbf{Ischemia} & \textbf{Statistics} \\
\hline
\textbf{Demographics} &  &  &  &  \\
Gender (M/F)* & 70/80 & 48/64 & 22/16 & NS \\
Age (yr) & 62 ± 12.4 & 60 ± 12.3 & 66 ± 12.2 & \textit{P} = 0.026 \\
\hline
\textbf{Preoperative risk evaluation} &  &  &  &  \\
Benign/malignant pathology* & 26/124 & 24/88 & 2/36 & \textit{P} = 0.03 \\
Bilirubin level (μg/L) & 16 ± 31 & 34 ± 89 & & NS \\
Fibrosis/absence of fibrosis* & 47/103 & 36/76 & 11/27 & NS \\
\hline
\textbf{Postoperative evolution} &  &  &  &  \\
Peak AST (IU/L) & — & 363 ± 34 & 861 ± 937 & \textit{P} < 0.001 \\
Peak ALT (IU/L) & — & 391 ± 365 & 891 ± 812 & \textit{P} < 0.001 \\
Biliary leakage* & 10 (6.6%) & 3 (2.7%) & 7 (18.4%) & \textit{P} < 0.001 \\
Mortality* & 3 (2%) & 2 (1.7%) & 1 (2.6%) & NS \\
\hline
\end{tabular}
\caption{Characteristics of Patients and Differences Between Those With and Without Ischemia}
\end{table}

\begin{table}[h]
\centering
\begin{tabular}{l|c|c|c|c|c|c}
\hline
\textbf{Univariate and Multivariate Analysis of Study Factors for Localized Hepatic Ischemia} & \textbf{No Ischemia} & \textbf{Ischemia} & \textbf{Odds Ratio (95\% CI)} & \textbf{Univariate, P} & \textbf{Multivariate, P} \\
\hline
\textbf{Gender (M/F)*} & 48/64 & 22/16 & 1.03 (0.49–2.19) & 0.92 & — \\
Age (yr) & 60 ± 12.3 & 66 ± 12.2 & 0.12 (0.02–0.7) & \textit{P} = 0.026 & NS \\
Benign/malignant pathology* & 24/88 & 22/36 & 4.9 (1.35–31.5) & \textit{P} = 0.03 & NS \\
Bilirubin level (μg/L) & 16 ± 31 & 34 ± 89 & 0.05 (0.008–1.2) & 0.09 & — \\
Fibrosis/no fibrosis* & 36/76 & 11/27 & 1.16 (0.53–2.69) & 0.71 & — \\
Major/minor hepatectomy* & 47/65 & 17/21 & 0.83 (0.42–1.89) & 0.76 & — \\
Standard/segmental hepatectomy* & 48/64 & 23/15 & 2.04 (0.97–4.4) & 0.06 & — \\
Cut surface (cm²) & 83.98 ± 5 & 96.28 ± 64 & 0.23 (0.01–3.52) & 0.28 & — \\
Weight of resected liver (g) & 470 ± 401 & 438 ± 330 & 1.85 (0.09–74) & 0.71 & — \\
Blood loss (mL) & 805 ± 83 & 673 ± 143 & 3.25 (0.23–90.1) & 0.25 & — \\
Number of RBCs transfused & 3 ± 2 & 2.6 ± 0.7 & 13.04 (0.2–386) & 0.27 & — \\
Pringle/no Pringle* & 55/57 & 21/17 & 1.28 (0.61–2.79) & 0.51 & — \\
\hline
\end{tabular}
\caption{Univariate and Multivariate Analysis of Study Factors for Localized Hepatic Ischemia}
\end{table}
number of RBC c transfused did emerge as significant factors. It does not seem therefore that induced hypotension by blood loss was a factor related to localized ischemia in our study. Intermittent Pringle maneuver, used in half of our patients, also had no significant impact on the occurrence of ischemia. The lack of a relationship between use of the Pringle maneuver and significant ischemic damage has been documented in other studies. Jaundice also was not associated with a statistically significant risk of ischemia although a trend was observed in the univariate analysis (P = 0.09). Most likely this factor did not reach the point of statistical significance as only 12 of our patients had a preoperative elevation in bilirubin level.

The suggestion that the presence of malignant tumors, or cirrhosis, could reduce susceptibility for liver ischemia was not confirmed as none of these factors were significant in our univariate and multivariate analysis.

Serum transaminases levels were significantly higher in patients with localized ischemia, a finding which could be considered validation of the radiologic diagnosis. These patients had a higher incidence of biliary leakage than patients without ischemia (18.4% vs. 2.7%). The overall incidence of biliary leakage in our patients was 6.6%, which is comparable to that reported in previous publications. Although biliary leakages were not severe and all resolved spontaneously, this complication significantly prolonged the hospital stay.

In conclusion, our study has shown that localized hepatic ischemia is detectable in a significant proportion of patients after hepatectomy. This complication is, in general, clinically silent, although it might be one of the underlying causes of postoperative biliary fistulas. The occurrence of localized ischemia seems independent from the type and the extent of hepatectomy. Postoperatively elevated transaminases should be an indicator to suspect the presence of localized ischemia. As the clinical evolution has been spontaneously favorable in all cases except one, we believe that clinical observation is sufficient to detect the rare patient with suspected postoperative localized ischemia that may require more aggressive treatment.

ACKNOWLEDGMENTS
The authors thank Costanzo Limoni, statistician, for reviewing the analysis.

REFERENCES

Discussions

Professor H. Bismuth: Every liver surgeon knows that after liver resection, he or she may observe some kind of discoloration at the edge of the liver resection but usually this is not important to the site. So the merit of your article is in its very precise description of this phenomenon in terms of extent, severity, and location. I have some questions. The first is about the mechanism of hypoperfusion. You said in the article that the anatomic line of division between the segments is not straight and, when we do a liver resection, of course it is difficult to remain exactly in the line of division between the 2 segments. This may explain the appearance of those small 1 or 2 cm areas of discoloration that we observe. However, as in the image you showed with a large vascularization defect, it is more than that. I think it is really a nonanatomic resection or a ligation of a pedicle that does not correspond with the part of the liver you have to resect.

The second question concerns the consequences. Of course, we understand that the transaminases are high and this is normal, but I am a little perplexed as to the explanation of the biliary leak. If there is only hypoperfusion of a part of the parenchyma, why should it result in a bile leak? If there really is a cause and effect relationship, then indeed, are the 2 phenomena not consequences of the same pedicle ligation?

Dr. R. Vandoni: As to your first question about the mechanism of ischemia, the intersegmental planes are virtual representations of the anatomy and it is difficult to know exactly where the transection should pass. Remaining ischemic parenchyma may explain the small area of ischemia visible on the edge of the resection. The other problem is that there are frequent variations of the modal distribution of the portal triads and this can cause unexpected ischemia on a nearby territory, especially when selective clamping cannot be applied before parenchyma transection. Finally, important variations of venous drainage are increasingly described but not necessarily recognized during surgery. The venous congestion resulting from interruption of a branch of a hepatic vein might translate into perfusion defects detectable on CT scans and mimicking inflow compromise.

It is difficult to answer your remarks concerning the cause of biliary leaks. One can, however, speculate that unless the section of the parenchyma is performed exactly in the intersegmental plane, small bile ducts will be cut. An inexact transection plane will leave unvascularized parenchyma but also with great probability remove vascularized parenchyma from a nearby segment. This may explain biliary leakages. As you mentioned, the unnoticed section of an abnormal portal triad will damage all its elements, including the corresponding bile duct, which may cause a bile leak.

Professor P.-A. Clavien: Although many surgeons have suspected the negative impact of areas of ischemia left after liver resection, you could demonstrate, through the use of CT scans performed within 48 hours of surgery in a relatively large series of patients, that ischemic liver tissue causes postoperative complications, such as bile leaks.

I would like to ask 3 questions. First, could you define what constitutes a bile leak in your study? Did you stratify bile leaks by severity? My second question relates to the definition of necrosis, which includes the presence of air in a “devascularized” area of the liver. The presence of air is rather a sign of infection in absence of bilio-enteric anastomosis. Could you comment on the definition of necrosis on CT imaging, and what happened in the follow-up of patients with the presence of air in a “nonperfused” area of the liver? My last question has to do with the clinical relevance of your study. I admire your careful analysis of the CT findings and their correlation with the occurrence of bile leaks. Unfortunately, due to the sample size, you could not establish risk factors for necrosis, such as the technique of transection of the liver parenchyma, the use of the Pringle maneuver, the type of resection, or the presence of underlying liver disease. On the basis of the results of your study, could you tell us what we may do differently?

Dr. R. Vandoni: Concerning the definition of biliary leakages, I would like to emphasize that in all patients, the abdomen was closed over a suction drain. We defined biliary leakage as drainage of bile persisting over 4 days, whatever the volume drained. We did not stratify leaks by severity and all healed spontaneously.

To your question related to the definition of necrosis and the presence of air bubbles in the liver, I can say that we observed such lesions in only 2 patients. One of them was operated on for hepatocellular carcinoma and the CT scan you saw was one of the latest in the series, having been performed 35 hours after heptatectomy. Indeed it is possible that the bubbles were related to infection and not to necrosis. It is also possible that the timing of CT scanning might have influenced the morphologic aspect of the lesion. The evolutions of patients with nonperfusion and patients with necrosis were similar. It may well be that we were looking at the same lesions, and observing them at different times of their evolution.

Finally, what could we do differently to reduce the incidence of biliary leaks? In our collective, we have seen that with ischemia, you have more biliary leaks. This would be an argument to decrease the risks of localized ischemia by precise preoperative planning of the limits of resection. This could perhaps be achieved by generalizing sophisticated 3-dimensional reconstructions as published by Lang and the Essen team.
PROFESSOR S. STRASBERG: I think one of the potential reasons why this sort of thing can happen is that, as Couinaud has shown us, in about 10% of patients structures entering the right anterior pedicle will actually be supplying parts of segment 6 or 7. That can become very confusing when a clamp is applied to the right anterior sectional pedicle. My question therefore is, was going through a particular plane more likely to result in a large area of ischemia? I think we all feel that the most difficult plane to go through in liver surgery reproducibly and accurately is the right intersectional plane, the plane between the right anterior and posterior sections.

DR. R. VANDONI: The answer is no, we could not identify a particular plane more likely to cause ischemia. The number and the distribution of the resections did not allow us to focalize our study on this particular aspect of the risk of ischemia.

PROFESSOR T. VAN GULIK: I have just a short question. Could you tell us something about the correlation of the intra-operative observations and your observations postoperatively on your imaging studies? Obviously, when you are doing a segment 7 resection and you see that segment 6 is nonperfused after that, you would take segment 6 out. So my question is, what were the remarks during the operation regarding the imaging results you acquired after the operation? Did you record that there was an ill-perfused part of the remnant liver and correlate that with what you saw later on the CT scan.

DR. R. VANDONI: I cannot give you the numbers but some of the marginal ischemia were expected. We could say that because we saw it during the operation. The severe ones, the segmental ones, were a surprise on the CT scan.

PROFESSOR P. GERTSCH: I would just like to clarify a few answers. Obviously, after hepatectomies, it is not rare to see discoloration on the edge of the resection. This does not tell us exactly what is happening in the depth of the liver and we undertook this study to clarify the real extent of postoperative ischemia. Now, I assume that there were different causes at the origin of the various types of ischemia we observed. We know the high variability in the anatomy of the liver and in the shape of its segments. Intersegmental planes are not flat, and they assume curved shapes that are often difficult to follow in the depths of the liver. What we see on the surface of the liver is not sufficient to guide our progression deep in the parenchyma. So we can assume that, in a few cases, the cut section left behind unvascularized parenchyma and also removed vascularized parenchyma, without necessarily compromising the main pedicle of the remaining segments.

Another important element is the increasing awareness of an extremely high variability in the anatomy of the hepatic veins. We see, with sophisticated 3-dimensional reconstructions as performed by Lang in Essen, that it is now possible to improve the planning of liver resections in predicting areas of postoperative hepatic congestion. With classic imaging technique and in the absence of such preoperative reconstructions, it is very likely that we unknowingly compromised the venous return in some liver areas. The radiologic expression of localized interruption of the venous return can produce images similar to some observed in our study, as shown by Wang in Seoul. So, I tend to think that some of our patients with partial ischemia that evolved into complete recovery experienced rather an interruption of the venous return than an in-flow interruption. Of course this is a speculative consideration.
Is There Still a Role for Total Pancreatectomy?

Michael W. Müller, MD,* Helmut Friess, MD,* Jörg Kleeff, MD,* Rolf Dahmen, MD,* Markus Wagner, MD,† Ulf Hinz, MSc,* Daniela Breisch-Girbig,* Güralp O. Ceyhan, MD,* and Markus W. Büchler, MD*

Objective: To evaluate the perioperative and long-term results of total pancreatectomy (TP), and to assess whether it provides morbidity, mortality, and quality of life (QoL) comparable to those of the pylorus-preserving (pp)-Whipple procedure in patients with benign and malignant pancreatic disease.

Summary Background Data: TP was abandoned for decades because of high peri- and postoperative morbidity and mortality. Because selected pancreatic diseases are best treated by TP, and pancreatic surgery and postoperative management of exocrine and endocrine insufficiency have significantly improved, the hesitance to perform a TP is disappearing.

Patients and Methods: In a prospective study conducted from October 2001 to November 2006, all patients undergoing a TP (n = 147; 100 primary elective TP [group A], 24 elective TP after previous pancreatic resection [group B], and 23 completion pancreatectomies for complications) were included, and perioperative and late follow-up data, including the QoL (EORTC QLQ-C30 questionnaire), were evaluated. A matched-pairs analysis with patients receiving a pp-Whipple operation was performed.

Results: Indications for an elective TP (group A + B) were pancreatic and peripancreatic adenocarcinoma (n = 71), other neoplastic pancreatic tumors (intraductal papillary mucinous neoplasms, neuroendocrine tumors, cystic tumors; n = 34), metastatic lesions (n = 8), and chronic pancreatitis (n = 11). There were 73 men and 51 women with a mean age of 60.9 ± 11.3 years. Median intraoperative blood loss was 1000 mL and median operation time was 380 minutes. Postoperative surgical morbidity was 24%, medical morbidity was 15%, and mortality was 4.8%. The relaparotomy rate was 12%. Median postoperative hospital stay was 11 days. After a median follow-up of 23 months, global health status of TP patients was comparable to that of pp-Whipple patients, although a few single QoL items were reduced. All patients required insulin and exocrine pancreatic enzyme replacements. The mean HbA1c value was 7.3% ± 0.9%.

Conclusion: In this cohort study, mortality and morbidity rates after elective TP are not significantly different from the pp-Whipple. Because of improvements in postoperative management, QoL is acceptable, and is almost comparable to that of pp-Whipple patients. Therefore, TP should no longer be generally avoided, because it is a viable option in selected patients.


Postoperative complications after pancreatic resection are mainly related to problems with the pancreatic anastomosis. Therefore, various techniques have been developed to deal with the pancreatic stump. To avoid pancreatic anastomosis-related complications completely, total pancreatectomy (TP) was introduced in 1954 by Ross and then by Porter in 1958. Besides avoiding of a pancreaticojejunal anastomosis, TP was also considered as an extension of oncologic radicality in pancreatic cancer patients. High local recurrence rates after a Whipple resection or a distal pancreatectomy suggested that pancreatic adenocarcinomas might develop multicentrically in the pancreatic gland. Therefore, TP was thought to reduce the risk of tumor recurrence. However, the expected clinical advantages after TP were limited. In 1960, Howard and Jordan reported a first series of patients with TP. The perioperative mortality rate of 37% indicated that TP is a high-risk operation with morbidity and mortality similar to or slightly higher than those of the classic Kausch-Whipple resection.

After the first enthusiasm over TP, the disadvantages of this surgical strategy became more obvious. Several centers reported perioperative mortality and morbidity rates equal to those of the Whipple operation, but no improvement in long-term survival. In addition, TP resulted in major metabolic problems. Insulin-dependent diabetes mellitus with unstable and difficult-to-control blood glucose levels contributed to significant morbidity and mortality in the long-term follow-up. Malabsorption was also difficult to control. High-quality enzyme formulations needed to overcome the problems of exocrine pancreatic insufficiency were not available. Therefore, weight loss, diarrhea, and malabsorption contributed to cachexia-like syndromes with significantly decreased quality of life (QoL) and physical activity. Pancreatic exocrine insufficiency in diabetic patients further aggravated the problems of blood glucose control. Steatorrhea also contributed to the loss of fat-soluble vitamins, especially vitamin D, leading to osteopathy and osteoporosis as well as liver disorders. Because of the tremendous postoperative metabolic

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966

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problems and the reduced QoL, without the advantages of oncologic radicality, TP was abandoned and no longer considered as a viable option for treating pancreatic tumors.

Today, major improvements in the control of diabetes mellitus and the development of modern pancreatic enzyme preparations with sufficient control of endocrine and exocrine pancreatic insufficiency provide options for overcoming the postoperative problems that follow TP. These developments make it possible to reconsider TP as a treatment option in pancreatic disorders in which organ-preserving resection is impossible because of the spread of the disease over the whole organ, or in which a pancreatic anastomosis cannot be safely performed because of the texture of the pancreatic parenchyma at the resection margin. Today, we more frequently diagnose patients in whom the whole gland is affected, eg, patients with intraductal papillary mucinous neoplasia (IPMN) or multiple metastasis of renal cell carcinomas; thus, the clinical need for TP is increasing.

In the present study we evaluated the perioperative results and long-term course of patients with TP to determine whether improvements in perioperative care have contributed to a favorable outcome and QoL after this operation.

PATIENTS AND METHODS

Patient Characteristics

Data of patients undergoing a TP between October 2001 and November 2006 in the Department of General Surgery, University of Heidelberg, Germany, were entered prospectively in an electronic database. One hundred twenty-four patients had an elective TP, whereas 23 patients underwent a completion TP because of severe pancreatic leakage after a pancreatic resection (first 2 years: 26 patients; second 2 years: 68 patients; last year: 53 patients). The mean age of all patients was 61.1 ± 11.5 years.

Indications for TP were pancreatic ductal adenocarcinoma, periampullary cancer, IPMN, cystic pancreatic tumors, neuroendocrine pancreatic tumors, metastatic lesions in the pancreas, and chronic pancreatitis (Table 1).

TP was performed as primary elective TP (n = 100), elective TP after pancreatic head or tail resection (n = 24), and completion pancreatectomy (n = 23) because of severe postoperative complications after partial pancreatic resection (Table 1).

Perioperative data, including operation time, intraoperative blood loss, blood transfusion, hospital mortality, total morbidity, relaparotomy, surgical morbidity, medical morbidity, intensive care unit (ICU) stay, and total postoperative hospital stay, were recorded (Table 2).

Follow-up

Patients were followed up in the outpatient clinic and interviewed using a standardized questionnaire. Nausea, vomiting, flatulence, constipation, diarrhea, appetite, weight, hospital readmission, pain, and subjective feeling were recorded.

In addition, QoL was assessed with the EORTC QLQ-C30 quality of life questionnaire, version 3.0. The questionnaire comprised both multi-item scales and single-item measures, including functional and symptom scales and global health status. A linear transformation was used to standardize the raw score, producing a score ranging from 0 to 100, with a high score representing a higher response level. Thus, a high score for a functional scale represents a high level of health. A high score for the global health status represents a high QoL, but a high score for a symptom scale represents a high level of symptomatology or problems.

Reference data were obtained from a healthy control, as reported previously.

Matched-Pairs Analysis

To evaluate whether the perioperative course and postoperative follow-up parameters, including QoL, were different for TP and pylorus-preserving (pp)-Whipple resection, a matched-pairs analysis of patients with primary elective TP was performed. Patients were matched for age, gender, and histology.

Statistical Analysis

SAS software (Release 9.1, SAS Institute, Inc., Cary, NC) was used for statistical analysis. QoL parameters from the QLQ-C30 questionnaire, as well as age and follow-up time are presented as mean with standard deviation and as median with range. Comparisons of groups of patients were performed using Fisher exact test. Continuous parameters were compared between groups of patients using the non-parametric Mann-Whitney U test. Overall survival from the date of surgery was estimated using the Kaplan-Meier method. Median survival and 1- and 3-year survival rates were presented. The log-rank test was performed to compare survival time distributions between the patient groups with benign and malignant disease. Patients alive at the last follow-up were censored and marked in the figure (represented by a solid line), as were 4 patients who were lost to follow-up.

Two-sided P values were always computed, and an effect was considered statistically significant at P < 0.05.

RESULTS

In a 5-year period (October 2001 to November 2006), 147 total pancreatectomies were performed. One hundred patients (68%) underwent primary elective TP. Twenty-four patients (16%) had a partial pancreatic resection (16 partial duodenopancreatectomy, 3 pancreatic left resection, 3 Beger procedure, 1 segmental pancreatic resection, and 1 cystojejunostomy) before TP and underwent TP electively because of recurrence of their primary disease. Twenty-three patients (16%) had a completion pancreatectomy because of severe postoperative complications after elective pancreatic resection (Whipple resection, n = 22; left resection and tumor enucleation in the pancreatic head, n = 1) (Table 1). Indications for completion pancreatectomy were leakage of the pancreatic anastomosis (n = 15), bleeding at the pancreatic anastomosis (n = 4), and necrosis of the pancreatic remnant (n = 4).

Thirty-three patients (22%) had TP for benign pancreatic disease and 114 patients (78%) were operated on because of malignant disorders (Table 1).
In the total cohort, splenectomy was performed in 67% of the patients. An attempt was always made to preserve the spleen when there was no oncologic need for splenectomy, because the potential for deterioration of the immunologic and hematologic function as well as a risk of portal thrombosis can accompany splenectomy. Portal vein or superior mesenteric vein resection was carried out in 26% of the patients. Twenty-six percent of these patients had a vascular reconstruction with a Gore-tex graft. In 56% of the patients undergoing TP the stomach and the pylorus were preserved (Table 1).

Median operation time in all patients undergoing elective TP was 380 minutes. Total hospital mortality was 4.8% (6 patients). In contrast, in patients with completion pancreatectomy, hospital mortality (9 patients; 39.1%) was massively increased because of severe postoperative complications. Hospital morbidity was 35.5% in all elective patients. Thirty patients (24%) developed surgical complications and 18 patients (14.5%) had medical complications (Table 2). Surgical and medical morbidity were also highest in patients with completion pancreatectomy, because of severe postoperative complications (Table 2). In all elective patients, postoperative hospital stay was a median of 11 days, including a median stay in the ICU of 3 days (Table 2).

Long-term survival was calculated for patients with benign and malignant disease from the date of surgery using

<table>
<thead>
<tr>
<th>Variable</th>
<th>Primary Elective TP (Group A)</th>
<th>Elective TP After Previous Pa-Res. (Group B)</th>
<th>Total Elective TP (Groups A + B)</th>
<th>Completion Pancreatectomy for Complications</th>
</tr>
</thead>
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<tr>
<td>Number</td>
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<td>124</td>
<td>23</td>
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<td>Age (yr)</td>
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<td>58.8 ± 12.7</td>
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<td>62.4 ± 10.4</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>55</td>
<td>18</td>
<td>73</td>
<td>15</td>
</tr>
<tr>
<td>Female</td>
<td>45</td>
<td>6</td>
<td>51</td>
<td>8</td>
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<td>Histology</td>
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<tr>
<td>Pancreatic adenocarcinoma</td>
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<td>10</td>
<td>67</td>
<td>11</td>
</tr>
<tr>
<td>Periampullary cancers*</td>
<td>4</td>
<td>—</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>IPMN</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignant</td>
<td>8</td>
<td>2</td>
<td>10</td>
<td>—</td>
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<tr>
<td>Borderline</td>
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<td>—</td>
<td>—</td>
<td>1</td>
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<td>8</td>
<td>3</td>
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<td>1</td>
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<tr>
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<tr>
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<td>—</td>
<td>4</td>
<td>1</td>
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<tr>
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<td>1</td>
<td>2</td>
<td>—</td>
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<tr>
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<td>—</td>
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<td>1</td>
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<tr>
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<td>5</td>
<td>3</td>
<td>8</td>
<td>—</td>
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<tr>
<td>Chronic pancreatitis</td>
<td>6</td>
<td>5</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>Portal vein/SMV resection</td>
<td>30 (30%)</td>
<td>3 (13%)</td>
<td>33 (27%)</td>
<td>5 (22%)</td>
</tr>
<tr>
<td>Splenectomy</td>
<td>66 (66%)</td>
<td>19 (79%)</td>
<td>85 (69%)</td>
<td>13 (57%)</td>
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<td>Pylorus-preserving TP</td>
<td>56 (56%)</td>
<td>8 (33%)</td>
<td>64 (52%)</td>
<td>18 (78%)</td>
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<td>Multivisceral resection</td>
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<td>4 (17%)</td>
<td>15 (12%)</td>
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<tr>
<td>Pain intensity</td>
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<td>None</td>
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<td>Weak</td>
<td>39</td>
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<td>8</td>
<td>3</td>
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<tr>
<td>Enzyme replacement</td>
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<td>2</td>
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<tr>
<td>Endocrine insufficiency</td>
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<td>8</td>
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<tr>
<td>ASA score</td>
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<tr>
<td>I</td>
<td>4</td>
<td>1</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>II</td>
<td>51</td>
<td>10</td>
<td>61</td>
<td>10</td>
</tr>
<tr>
<td>III</td>
<td>45</td>
<td>13</td>
<td>58</td>
<td>12</td>
</tr>
</tbody>
</table>

*Without pancreatic head cancer.

TP indicates total pancreatectomy; Pa-Res, pancreatic resection; IPMN, intraductal papillary mucinous neoplasia; SMV, superior mesenteric vein; BMI, body mass index; ASA, American Society of Anesthesiologists.
the Kaplan-Meier method. Four patients were regarded as lost for follow-up (alive at last follow-up before January 2005; this follow-up time was used for the survival analysis). Forty-three patients were dead at the follow-up (3 with benign disease, 40 with malignant disease). Among patients with malignant disease, the median survival was 21.9 months, and the 1-year and 3-year survival rates were 64.3% and 36.6%, respectively (Fig. 1). In the group of patients with benign pathology, 30 patients are alive, and therefore no median survival was calculable. The 1-year and 3-year survival rates were both 88.3% (Fig. 1).

For long-term follow-up, only patients with an elective TP (n = 124) and a postoperative follow-up period of longer than 6 months were included. Six patients died in hospital because of complications, 18 patients had a follow-up time less than 6 months, 21 patients died in the follow-up, and 12 were not available for follow-up; that left 47 patients with malignant disease and 20 patients with benign disease who could be included in the long-term follow-up.

The HbA1c level was different (P < 0.05) between the patients with benign (6.7% ± 0.9%) and with malignant disease (7.5% ± 0.9%). Hospital readmission because of

![Figure 1](https://example.com/figure1.png)
diabetes mellitus-related problems and for adjustment of the insulin therapy occurred in 4 patients with benign disease (hyperglycemia 1 patient, hypoglycemia 3 patients) and in 7 patients with malignant disease (hyperglycemia 4 patients, hypoglycemia 3 patients). However, there was no life-threatening diabetes-related problem.

Significantly more patients (P < 0.05 and P < 0.01) with malignant disease complained of flatulence (28 patients, 60%) and diarrhea (30 patients, 64%) compared with the patients with benign disease (flatulence in 6 patients, 30%, and diarrhea in 2 patients, 10%). No significant difference was observed for nausea, vomiting, constipation, pain frequency, pain intensity, subjective feeling, appetite, weight increase, weight loss, and body mass index.

With regard to QoL, for most items there was also no difference between patients with benign and malignant disease. However, emotional functioning was significantly better in patients with benign disease compared with patients with malignant disease (76.7 ± 24.9 vs. 63.1 ± 24.1; P < 0.05). In contrast, constipation was significantly worse in patients with benign disease than in patients with malignant disease (13.3 ± 25.1 vs. 4.2 ± 16.5; P < 0.05). In comparison with a normal German control population,14 patients after TP showed a tendency for lower global health status and function scales. However, only the symptom scales for diarrhea were clinically significantly worse in patients after TP.

**Matched-Pairs Analysis**

To evaluate the clinical outcome of patients with primary elective TP (n = 100) and no metastatic disease (n = 93), a matched-pairs analysis including patients with pp-Whipple operated on in the same time period was performed. Only patients who had a follow-up time longer than 6 months were included (n = 87). Patients were matched for age, gender, and histology. Eighty-seven pairs could be formed, as previously described.17 In this patient cohort, perioperative patient parameters were analyzed and compared. Of the patients in these pairs, 21 patients with primary elective TP and 23 patients with pp-Whipple died in the follow-up. In addition, 11 patients with primary elective TP and 10 patients with pp-Whipple were lost for follow-up. Of all available patients, 46 pairs were available for clinical as well as QoL evaluation.

Matched-pairs analysis of 87 pairs revealed no difference in American Society of Anesthesiologists score, mortality, total morbidity, surgical morbidity, medical morbidity, or hospital stay (Table 3). However, there was a significant difference in operation time, intraoperative blood loss, blood transfusion, and ICU stay between the 2 groups (Table 3).

Long-term follow-up in the 46 matched-pairs revealed no difference with regard to constipation, appetite, body mass index, weight change, pancreatic enzyme substitution, pain, or subjective feeling (Table 4). In contrast, patients with primary elective TP suffered more often from diarrhea. In addition, patients with pp-Whipple required significantly less frequent insulin substitution (Table 4).

### TABLE 3. Matched-Pairs Analysis: Characteristics of 87 Patients With Primary Elective TP and 87 Patients With pp-Whipple

<table>
<thead>
<tr>
<th>Variable</th>
<th>Primary Elective TP (n = 87)</th>
<th>pp-Whipple (n = 87)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)*</td>
<td>63.8 (54.5–69.2)</td>
<td>63.5 (55.7–68.2)</td>
<td>n.s.</td>
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<td>Gender</td>
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<td>n.s.</td>
<td></td>
</tr>
<tr>
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<td>40</td>
<td>40</td>
<td>n.s.</td>
</tr>
<tr>
<td>Female</td>
<td>47</td>
<td>47</td>
<td>n.s.</td>
</tr>
<tr>
<td>Tumor entity</td>
<td>n.s.</td>
<td>n.s.</td>
<td></td>
</tr>
<tr>
<td>Malignant</td>
<td>80</td>
<td>80</td>
<td>n.s.</td>
</tr>
<tr>
<td>Benign</td>
<td>7</td>
<td>7</td>
<td>n.s.</td>
</tr>
<tr>
<td>ASA score</td>
<td>n.s.</td>
<td>n.s.</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>3</td>
<td>3</td>
<td>n.s.</td>
</tr>
<tr>
<td>II</td>
<td>45</td>
<td>54</td>
<td>n.s.</td>
</tr>
<tr>
<td>III</td>
<td>39</td>
<td>30</td>
<td>n.s.</td>
</tr>
<tr>
<td>Operation time (min)*</td>
<td>385 (337–435)</td>
<td>359 (300–420)</td>
<td>&lt;0.05†</td>
</tr>
<tr>
<td>Intraoperative blood loss (ml)*</td>
<td>1000 (700–1700)</td>
<td>500 (400–850)</td>
<td>&lt;0.01†</td>
</tr>
<tr>
<td>Blood transfusion (units)*</td>
<td>2 (0–4)</td>
<td>0 (0–0)</td>
<td>&lt;0.01†</td>
</tr>
<tr>
<td>Mortality</td>
<td>6</td>
<td>3</td>
<td>n.s.</td>
</tr>
<tr>
<td>Total morbidity</td>
<td>32</td>
<td>23</td>
<td>n.s.</td>
</tr>
<tr>
<td>Surgical morbidity</td>
<td>21</td>
<td>13</td>
<td>n.s.</td>
</tr>
<tr>
<td>Medical morbidity</td>
<td>13</td>
<td>12</td>
<td>n.s.</td>
</tr>
<tr>
<td>Intensive care stay (d)*</td>
<td>3 (2–5)</td>
<td>1 (1–2)</td>
<td>&lt;0.01†</td>
</tr>
<tr>
<td>Postoperative hospital stay (d)*</td>
<td>11 (8–16)</td>
<td>12 (10–14)</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

*Median values with interquartile range are given.
†Wilcoxon test.

Analysis of QoL revealed differences in the functional scale and the symptom scale but not in global health status (Table 5). At a median follow-up of 23 months, patients with TP had a significantly lower functional scale, role functioning, and social functioning and a worse symptom scale and financial strain score (Table 5).

### DISCUSSION

In the early 1950s, when pancreatic resection was associated with considerable morbidity as well as mortality rates of up to 50%, surgeons introduced TP to avoid anastomosis-related complications, which are normally the starting point for hospital mortality. In addition, high local recurrence rates after partial pancreaticoduodenectomies supported the idea that through more radical resection, long-term survival for pancreatic malignancies could be improved.14,18 However, in practice, use of TP to reduce hospital mortality and improve prognosis proved disappointing.1 Therefore, TP was abandoned by many surgeons as a standard operation for pancreatic disease. An additional major argument against TP was that it led to insulin-dependent diabetes mellitus, which was difficult to control in many of these patients. Fear of performing TP was especially increased by reports of patients with brittle diabetes mellitus.9

Severe malabsorption because of the complete loss of exocrine pancreatic secretion was another major argument against TP. Malabsorption related to exocrine pancreatic
TABLE 4. Matched-Pairs Analysis of Patients With Primary Elective TP and pp-Whipple Who Were Available for Long-term Follow-up (46 Pairs)

<table>
<thead>
<tr>
<th></th>
<th>Primary Elective TP (n = 46)</th>
<th>pp-Whipple (n = 46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>61.2 ± 11.7</td>
<td>61.6 ± 11.1</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>27</td>
<td>28</td>
</tr>
<tr>
<td>Female</td>
<td>19</td>
<td>18</td>
</tr>
<tr>
<td>Tumor entity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignant</td>
<td>32</td>
<td>32</td>
</tr>
<tr>
<td>Benign</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Follow-up period (mo)</td>
<td>23.7 ± 12.2</td>
<td>24.9 ± 12.8</td>
</tr>
<tr>
<td>Constipation</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Appetite</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>35</td>
<td>33</td>
</tr>
<tr>
<td>Moderate</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Bad</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.7 ± 3.2</td>
<td>24.3 ± 6.2</td>
</tr>
<tr>
<td>Weight</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Median (range), kg</td>
<td>7 (1.5–15)</td>
<td>8 (1–10)</td>
</tr>
<tr>
<td>Unchanged</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td>Loss</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>Median (range), kg</td>
<td>13.5 (6–30)</td>
<td>8.5 (1–25)</td>
</tr>
<tr>
<td>Enzyme substitution</td>
<td>46</td>
<td>43</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>46</td>
<td>11</td>
</tr>
<tr>
<td>Pain intensity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>23</td>
<td>32</td>
</tr>
<tr>
<td>Weak</td>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td>Moderate</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Severe</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Subjective feeling</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very good</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Good</td>
<td>28</td>
<td>25</td>
</tr>
<tr>
<td>Moderate</td>
<td>14</td>
<td>13</td>
</tr>
<tr>
<td>Major complaint</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

TABLE 5. Matched-Pairs Analysis of Quality of Life in Patients With Primary Elective TP and pp-Whipple Who Were Available for Long-term Follow-up (46 Pairs)

<table>
<thead>
<tr>
<th></th>
<th>Primary Elective TP (n = 46)</th>
<th>pp-Whipple (n = 46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality of Life Evaluation (EORTC QLQ-C30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global health status</td>
<td>60.7 ± 19.5</td>
<td>67.0 ± 20.2</td>
</tr>
<tr>
<td>Quality of life assessment: function scales</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Functional scale</td>
<td>73.0 ± 18.3*</td>
<td>79.8 ± 18.8</td>
</tr>
<tr>
<td>Physical functioning</td>
<td>77.4 ± 22.7</td>
<td>80.2 ± 21.7</td>
</tr>
<tr>
<td>Role functioning</td>
<td>67.0 ± 28.7*</td>
<td>79.9 ± 29.0</td>
</tr>
<tr>
<td>Emotional functioning</td>
<td>69.7 ± 21.8</td>
<td>72.7 ± 22.8</td>
</tr>
<tr>
<td>Cognitive functioning</td>
<td>80.4 ± 25.7</td>
<td>81.4 ± 23.3</td>
</tr>
<tr>
<td>Social functioning</td>
<td>66.7 ± 31.6*</td>
<td>89.3 ± 18.8</td>
</tr>
<tr>
<td>Quality of life assessment: symptom scales</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptom scale</td>
<td>22.0 ± 15.1*</td>
<td>18.5 ± 17.8</td>
</tr>
<tr>
<td>Fatigue</td>
<td>37.7 ± 26.0</td>
<td>31.6 ± 28.5</td>
</tr>
<tr>
<td>Nausea, vomiting</td>
<td>6.2 ± 16.6</td>
<td>4.3 ± 14.5</td>
</tr>
<tr>
<td>Pain</td>
<td>22.8 ± 26.6</td>
<td>20.1 ± 36.7</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>13.8 ± 24.9</td>
<td>9.6 ± 21.2</td>
</tr>
<tr>
<td>Insomnia</td>
<td>29.0 ± 30.3</td>
<td>27.2 ± 33.7</td>
</tr>
<tr>
<td>Appetite loss</td>
<td>15.6 ± 27.2</td>
<td>16.7 ± 30.2</td>
</tr>
<tr>
<td>Constipation</td>
<td>8.0 ± 21.3</td>
<td>10.9 ± 28.4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>28.1 ± 32.5</td>
<td>26.9 ± 33.0</td>
</tr>
<tr>
<td>Financial strain</td>
<td>20.3 ± 26.7*</td>
<td>5.0 ± 17.8</td>
</tr>
</tbody>
</table>

*P < 0.05.

insufficiency contributed further to poor blood sugar control. Loss of exocrine pancreatic secretion, with subsequent diarrhea, steatorrhea, and short food transit time, resulting in inestimable carbohydrate absorption, made it difficult to adapt the insulin dose to the food intake. Furthermore, exocrine pancreatic insufficiency-related steatorrhea, with subsequent weight decrease and loss of fat-soluble vitamins, contributes to osteoporosis, hepatic dysfunction, and other disorders.9

Although a pancreatic anastomosis is avoided in TP, early clinical studies on TP reported hospital mortality rates of up to 40%, which was in some series even higher than after partial pancreatic resection. In recent years, however, hospital morbidity and mortality after major resection of the pancreas have decreased continuously because of better anastomosis technique and better postoperative care, and TP—although a much more extensive operation—can be offered with the same operation risk as a Whipple resection.8,19–21 Thus, surgeons are no longer afraid to perform TP.

Clinically, the need for TP has increased over the years. Extension of resection criteria in pancreatic malignancies and our current knowledge of specific disease entities of the pancreas—such as IPMNs, which are premalignant lesions often affecting the whole pancreas—require TP.22–24 In addition, patients with a family history of hereditary pancreatic cancer, patients suffering from hereditary chronic pancreatitis, and patients with other known diffuse premalignant lesions in the pancreas have a considerable risk of developing pancreatic cancer during their lifetime.25 Although clear risk data are lacking, it is estimated that patients with hereditary chronic pancreatitis have a 50- to 70-fold increased risk of developing pancreatic cancer compared with a control population. TP is a prophylactic measure in high-risk populations,26 used to eliminate the risk of cancer development, as for premalignant lesions (eg, total proctocolectomy in patients with familiar adenomatous polyposis of the colon).27

However, the fact that TP leads to insulin-dependent diabetes mellitus induction, with subsequent secondary diabetes-related morbidity and poor QoL, makes prophylactic TP questionable. Presently, there is agreement that TP is an option to prevent pancreatic cancer. However, the timing and extent of surgery are still controversial. Because pancreatic cancer has an extremely poor prognosis and poor survival after curative resection, there is a clear argument for TP in these patients. Therefore, it is essential that we evaluate long-term outcome and QoL in patients with TP on the basis...
of modern diabetes mellitus treatment, control of exocrine pancreatic insufficiency with modern pancreatic enzyme formulations, and our knowledge that fat-soluble vitamins have to be controlled and substituted in these patients.

In the present study we have presented the data from 147 patients who underwent TP in the last 5 years. Thirty-six percent of the patients in this series underwent operation within the last year, indicating the increasing demand for TP. Sixty-eight percent of the patients received a primary elective TP, 16% an elective TP after previous pancreatic resection, and 16% a completion pancreatectomy because of in-hospital occurrence of severe operation-related complications, mainly after a Whipple resection. In elective TP patients, hospital mortality was below 5% and morbidity below 40%, which compares well with the outcome of partially or totally pancreatectomized patients. Therefore, one conclusion of our study is that elective TP can be performed with morbidity and mortality not significantly different from that of less-extensive pancreatic resections, a conclusion supported by our matched-pairs analysis comparing pp-Whipple and TP. However, TP is a more radical and extensive procedure, outlined in our matched-pairs analysis by a significantly longer operation time and greater intraoperative blood loss, with a correspondingly higher need for blood transfusion. Specifically, the mean operation time was 26 minutes longer, and the mean blood loss increased from 500 to 1000 mL in the primary elective TP group compared with the pp-Whipple group in the matched-pairs analysis. The increased blood loss and operation time in the TP group might be because of more extensive preparation, more advanced disease, and more difficult intraoperative decision-making including multiple frozen sections in some cases. Furthermore, a significantly longer ICU stay after TP supported this finding. Admittedly, completion pancreatectomy for complications had a 39% mortality rate and a high morbidity rate. In the recent literature, mortality rates after completion pancreatectomy range from 0% to 67%. The reason for this wide range of mortality might include different indications for completion pancreatectomy like bleeding or leakage in different institutions. Furthermore, the timing to perform a completion pancreatectomy might have an important influence as well. This might be the fact in our institution, because the indication for completion pancreatectomy is given only when the clinical situation of the patient with a severe complication after a pancreatic resection is bad and conservative treatment strategies have been exhausted.

Because a major argument against TP was that it reduced QoL because of diabetes mellitus and metabolic disturbances, we also evaluated this in our matched-pairs analysis. QoL was assessed only in patients with a follow-up time of longer than 6 months postoperatively to have a more homogenous patient cohort with regard to QoL aspects. After major pancreatic resections most patients need several months for recovery and adaptation to the new metabolic situation. Furthermore, many patients with malignant tumors receive adjuvant chemotherapy, which normally starts in the first 4 weeks after surgery and normally takes up to 6 months. Therefore, the potentially negative effect of the chemotherapy on the QoL parameters was omitted.

Some QoL parameters were reduced in patients after primary elective TP compared with pp-Whipple patients. However, global health status was not different between the patient cohorts, indicating that both operations achieve a comparable and satisfying QoL. Admittedly, the drawback of the matched-pairs analysis is the limited number of patients who were available for the long-term follow-up because of death, as well as the loss of follow-up in either group leading to the exclusion of matched pairs.

Our findings are supported by a recent study from the Mayo Clinic in which QoL was assessed in 34 patients with TP at a mean follow-up of 7 years. Although in the Mayo study QoL after TP was decreased compared with age- and gender-matched controls, comparison with patients with diabetes mellitus from other courses revealed no difference. The glycemic control in our cohort was comparable to that of a recent study that reported mean HbA1c level of 7.4%, exactly the same as in our patients, and this level is lower than that shown in other series of TP. It reflects glycemic control close to that advocated for decreasing the risk of diabetic complications. In the follow-up, hospital readmission because of diabetes mellitus-related problems occurred in 16% of the patients. However, none of these patients had life-threatening diabetes-related problems. Therefore, the risk of hospitalization secondary to hypoglycemia or hyperglycemia in our study was in the range of a recently published series of TP and is in the range of patients with insulin-dependent diabetes from other causes.

Survival rates for TP patients with malignant pathology were similar to that of a recently published series and to that of patients undergoing a pancreatoduodenectomy for ductal adenocarcinoma. Furthermore, survival after TP for benign disease was similar to that previously published in patients with TP or partial pancreatectomy.

An interesting finding in our cohort of patients with TP was that in patients who have previously undergone partial pancreatic resection, removal of the remaining pancreas can be safely performed. Twenty-one percent of these patients had chronic pancreatitis, with a Beger procedure being performed in 3 patients, and a cystojejunostomy and a segmental pancreatic resection each in 1 patient, before TP. Sixty-seven percent of the patients had a previous pancreatic head resection, and therefore further anastomoses were not required. This might be the reason why in these 24 patients TP could be performed without mortality and with a low 21% morbidity compared with the other TP patients.

In conclusion, our study underlines that elective TP leads to perioperative mortality and morbidity comparable to that of other pancreatic resection procedures. Despite limitations caused by the ensuing insulin-dependent diabetes mellitus, the overall QoL is acceptable, and the limitations do not justify avoiding TP in patients in whom the complete removal of the pancreas is required for oncologic, technical, prophylactic, or complication-related reasons. Therefore, TP should
no longer be generally avoided, because it is a viable option in selected patients.

REFERENCES


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Discussions

Prof. D. Gouma: I endorse the final conclusion that total pancreatectomy is indicated for a selected group of patients but I still have a few comments and questions.

Is it justified to analyze this group of patients as one entity of patients including such a wide variety of indications for surgery? And do you not need different end points to analyze the final results of these different patient populations? For example, for patients with leakage after a Whipple procedure, you should look primarily for short-term survival after such a complication. But if you analyze a selected group of patients with adenocarcinoma or recurrent adenocarcinoma, you should focus on long-term survival in this particular group of patients and, of course, the percentage of R0 resections obtained to justify surgery for recurrent disease. For chronic pancreatitis, you should analyze pain control because that is the main indication for surgery in that group of patients. And for the other patients with benign disease, you should look for quality of life. So, is it indeed justified to analyze these patients as one group?

If you allow me, I would like to go into more detail in one group of patients. For example, in the particular group of patients with leakage and completion pancreatectomy, I was somewhat surprised by the numbers and outcome. A few years ago, we analyzed the data from Amsterdam showing that there was indeed an indication for completion pancreatectomy in selected patients and your chairman, Professor Büchler, mentioned that, in fact, there is no indication any more for completion pancreatectomy because leakage was no longer a problem. So, were these 23 patients collected in the last 3 or 4 years and why was there a change in the strategy? Another important finding is that the mortality was 39% in that particular group of patients, which is extremely high. These percentages are found in the older literature but nowadays, if you follow an aggressive approach that means surgery after a few days, the mortality rate, even after completion pancreatectomy, is low. What was the time frame between the first operation and the completion pancreatectomy?

If you look in more detail of all patients, the hospital mortality rate is still 9.3%, which is substantially higher compared with partial pancreatectomy and not the same as suggested. The reoperation rate for patients after total pancreatectomy was 20%, and for patients undergoing a Whipple procedure will be around 5%. So, despite the fact that the overall surgical complication rate is not higher after total pancreatectomy, the number of reoperations is extremely high compared with the Whipple procedures. Do you have an explanation for this difference?

Lastly, looking to the very sophisticated matched-pairs analysis of quality of life, you analyzed only 46 patients; so there might be a bias in selection in this group of patients. For example, patients dying from hypoglycemia outside the hospital are, of course, not included in this group. And if you look in detail at the analysis of those patients, you mentioned that the quality of life is roughly the same but social functioning was much lower after total pancreatectomy. Could this be because of the 40% of patients who suffered from severe diarrhea after total pancreatectomy? And, again, 40% of these patients experienced severe weight loss up to 35 kg. Are you sure that quality of life is exactly the same in that group of patients?

Dr. M. Müller: You are right; this is not a homogeneous patient group. We combined and evaluated different patient groups and we also conducted a follow-up and compared patients with malignant and benign disease. We could show that the survival in the Kaplan-Meier analysis was in accordance with patients with adenocarcinoma who received a Whipple or pylorus-preserving Whipple resection as well. Certainly, patients with benign disease had a better outcome and they had a 1-year and 3-year survival rate of 88%.

The difficulty regarding pain in patients with chronic pancreatitis was that we had only 14 patients with chronic pancreatitis. This makes the group too small for comparisons and statistical evaluations. So we used only the group of patients who underwent primary elective total pancreatectomy for further evaluation, but included all different diagnoses and compared it with pp-Whipple patients who were completely matched for histology, age, and gender. Therefore, in this matched-pairs analysis we really compared exactly the same diagnoses in these patients. We found no significant difference in the total quality of life. For sure, all these patients had diabetes mellitus and this reduces the quality of life. Landoni et al (J Pancreas. 2004;5:441.) and Billings et al (J Gastrointest Surg. 2005;9:1059–1066) showed that after total pancreatectomy diabetes mellitus reduces quality of life, but regarding global quality of life, there was no difference compared with other patients with diabetes mellitus.

Regarding pancreatic leakage after a pancreatic resection, normally we would not do a completion pancreatectomy in these patients per se. We would first like to perform a drainage in these patients. However, the patients in our study represent a selection of patients who did clinically very poorly. So in these patients we decided, after a period in the intensive care unit, to go on and perform total pancreatectomy. This is, again, a negative selection of patients with a complication, which probably explains these bad results. The time between the first operation and the completion pancreatectomy was, on average, 10 days for all patients in this
group; however, the patients with severe postoperative hemorrhage had a much lower time frame.

We lost some patients for follow-up and we have no information about them. However, in the matched-pairs analysis there were no reported deaths related to diabetes problems. All of the patients who died, either in the pylorus-preserving Whipple group or in the total pancreatectomy group, died because of malignant disease. All deaths in the total pancreatectomy group or in the pylorus-preserving Whipple group resulted in the discharge of that pair, leading to a reduction of pairs from 87 to 46.

PROF. K. CONLON: I agree with your conclusion that a total pancreatectomy is an option in selected patients but I have a comment and a question.

The comment is regarding the question “can we do it?” The answer is “yes.” “Should we do it?” The answer is “maybe.” I had the opportunity a number of years ago to review the Memorial Sloan Kettering data for total pancreatectomy for patients with adenocarcinoma of the pancreas and the median survival rate was only 7.4 months. So, in many cases, the oncologic impact is limited.

But my question relates to your follow-up and end points assessed. In the current study the follow-up is about 2 years and you focus on diabetes mellitus as your endocrine end point. But, of course, when we do a total pancreatectomy, we are removing the counter-regulatory hormones as well. And one of the long-term side effects for patients with total pancreatectomy is hepatic dysfunction. If one recommends this as a prophylactic procedure or a procedure for patients who have borderline malignancy, long-term survival may be compromised. I wonder whether you have had any evidence of liver dysfunction.

DR. M. MÜLLER: Unfortunately, we have just the endocrine function measured by the hemoglobin A1C levels, which were pretty good in the patient group with benign disease. In this group the hemoglobin A1 level was 6.7 and, in the other group with malignant patients, it was 7.3. So it was in a good range and we can show that there is good diabetes control in these patients. Still, we have no longer follow-up and we cannot comment on problems in liver failure. If you have good diabetes control, you might reduce this risk as well but I cannot give you more data on this topic.

PROF. M. BUHLER: I would like to offer just an explanation because one of the criticisms was directed to me. Yes, Professor Gouma, you are right. In the article we published in Archives of Surgery in 2003, we were too optimistic in saying that completion pancreatectomy is probably something of the past. During my time in Switzerland, we operated on 60 to 80 patients per year and, during that time, we did not in fact need completion pancreatectomy—it was a very rare event. Since we have been in Heidelberg, where we do 300 to 400 resections per year, we need completion pancreatectomy more often. In fact, I was too optimistic.
Unilateral Versus Bilateral Neck Exploration for Primary Hyperparathyroidism

Five-Year Follow-up of a Randomized Controlled Trial

Johan Westerdahl, MD, PhD, and Anders Bergenfelz, MD, PhD

Objective: To compare long-term patient outcome in a prospective randomized controlled trial between unilateral and bilateral neck exploration for primary hyperparathyroidism (pHPT).

Summary Background Data: Minimal invasive and/or focused parathyroidectomy has challenged the traditional bilateral neck exploration for pHPT. Between 1997 and 2001, we conducted the first unselected randomized controlled trial of unilateral versus bilateral neck exploration for pHPT. The results showed that unilateral exploration is a surgical strategy with distinct advantages in the early postoperative period. However, concerns have been raised that limited parathyroid exploration could increase the risk for recurrent pHPT during long-term follow-up.

Methods: Ninety-one patients with the diagnosis of pHPT were randomized to unilateral or bilateral neck exploration. Preoperative scintigraphy and intraoperative parathyroid hormone measurement guided the unilateral exploration. Gross morphology and frozen section determined the extent of parathyroid tissue resection in the bilateral group. Follow-up was performed after 6 weeks, 1 year, and 5 years postoperatively.

Results: Seventy-one patients were available for 5-year follow-up. There were no differences in serum ionized calcium and parathyroid hormone, respectively, between patients in the unilateral and bilateral group. Overall 6 patients have been found to have persistent (n = 3) or recurrent (n = 3) pHPT; 4 patients in the unilateral group (3 of these 4 patients were bilaterally explored) and 2 patients in the bilateral group. Three of 6 failures were unexpectedly found to have multiple endocrine neoplasia mutations. One patient with solitary adenoma in the bilateral group still required vitamin D substitution 5 years after surgery.

Conclusion: Unilateral neck exploration with intraoperative parathyroid hormone assessment provides the same long-term results as bilateral neck exploration, and is thus a valid strategy for the surgical treatment of pHPT.

(Am Surg 2007;246: 976–981)
Planned Intervention

A flow chart summarizing the study is shown in Figure 1. In short, 47 patients were randomized to the unilateral group (study group) and 44 patients to the bilateral group (control group). After randomization, patients in the study group underwent preoperative sestamibi subtraction scintigraphy. All patients underwent surgery, performed with general anesthesia, through a short (<5 cm) conventional Kocher incision. The strap muscles were dissected in the midline and not divided.

In the unilateral group, the preoperative scintigram and the measurement of ioPTH were used to guide the operation. Surgery started on the side indicated by the scintigram. If the scintigram was negative, the left side was explored first. In the bilateral group, surgery was started on the left side and comprehensive bilateral exploration was performed attempting to visualize all 4 parathyroid glands. The decision to terminate surgery was based on gross morphology in combination with frozen section.

Evaluation

All patients stayed overnight in the hospital. After the first postoperative day they were kept in the patient’s hotel of the hospital from day 2 to 4 because the initial postoperative follow-up was done from day 1 to 4. Thereafter, follow-up was performed after 6 weeks, 1 year, and 5 years postoperatively with biochemistry and with registration of complications. The results up to 6 weeks after the operation have been presented previously. Persistent pHPT was defined as hypercalcemia and high PTH levels occurring any time within the first 6 months after surgery. The occurrence of hypercalcemia and high PTH levels (without renal failure) after a documented period of postoperative normocalcemia, lasting at least 6 months, was classified as recurrent pHPT.

ioPTH Measurement

Serum PTH was analyzed intraoperatively in the unilateral group. The criteria used to determine when to terminate the neck exploration have been described previously. A decrease of 15 minutes after excision of an enlarged parathyroid gland of 60% or more below the baseline value (obtained when the first enlarged gland is visualized) reliably predicts a solitary parathyroid adenoma and early and late operative success.

Histopathology

The diagnosis of a parathyroid adenoma and hyperplasia was established by conventional histologic criteria, aided by gross morphology in the bilateral group and preoperative decrease in ioPTH in the unilateral group.

Renal Function

Glomerular filtration rate was measured using a method for the calculation of plasma clearance of the contrast agent iohexol. The reference values are 20 to 50 years, 80 to 125 mL/min; 51 to 65 years, 60 to 110 mL/min; and 66 to 80 years, 50 to 90 mL/min.

Biochemical Variables

All blood samples were drawn after an overnight fast. Preoperative data obtained from blood samples were collected the day before surgery.

Serum levels of calcium (reference range 2.20–2.60 mmol/L), alkaline phosphatase (reference range 0.8–4.6 μkat/L), phosphate (reference range 0.70–1.30 mmol/L), and creatinine (reference range in men 55–116 μmol/L and in women 45–100 μmol/L) were analyzed with routine autoanalyzer (Kodak Ektachem, 700xR-C, Eastman Kodak Co., Rochester, NY). Serum ionized calcium concentrations were analyzed from blood samples normalized to a pH of 7.4 with the ion-selective electrode ABL 505 (Radiometer, Copenhagen, Denmark) (reference range 1.15–1.35 mmol/L). Serum level of intact PTH was measured with the intact PTH assay (Inkster, Stillwater, Minn) (reference range 1.0–5.0 pmol/L). High-performance liquid chromatography was used for assessment of 25-hydroxycholecalciferol (25 (OH) D3) (reference range 20–100 nmol/L) and a radio-receptor assay (Inkster, Stillwater, Minn) for measurement of 1,25-dihydroxycholecalciferol (1.25 (OH)2 D3) (reference range 36–120 pmol/L).

Sample Size

The sample size of the study was calculated for early postoperative mediation for hypocalcemia. With a type 1 error of 0.05 (2-tailed) and a power of 0.80, it was determined that 44 patients in each group would be sufficient to detect a difference in oral calcium ingestion between the 2 groups.
Statistics

Analysis of outcome for the unilateral and bilateral group was done on an intention-to-treat basis. For numeric data difference between the groups were analyzed with the Mann-Whitney U test. For categorical data, statistical significance was analyzed using the \( \chi^2 \) test and the Fisher exact test when expected frequencies were less than 5. A probability level of a random difference of \( P < 0.05 \) was considered significant. Results for continuous variables are reported as median and range if not stated otherwise. For categorical data, absolute numbers in addition to percentage are given.

RESULTS

At surgery, 40 patients in the bilateral group had a solitary adenoma and 4 patients multiglandular disease. In the unilateral group, 41 patients had a solitary adenoma and 5 patients multiglandular disease. In 1 patient with negative sestamibi scan, a 3.5 gland resection was made due to suspicion of diffuse hyperplasia. However, conventional histopathology showed normal glands. The patient has persistent pHPT and declined further investigation. Twenty-nine of 47 patients in the unilateral group underwent unilateral exploration (62%). The results up to 6 weeks after the operation have been previously reported.

Long-term biochemical data and renal function are presented in Table 1. As can been seen there were no differences between the 2 groups in the analyzed biochemical variables 1 year or 5 years after surgery. At 5 years, the median (range) serum ionized calcium level was 1.23 mmol/L (1.10–1.39 mmol/L) in the bilateral group and 1.23 mmol/L (1.11–1.38 mmol/L) in the unilateral group. Sixty-seven of 71 patients had normal or slightly decreased serum ionized calcium levels. The median (range) serum PTH level was 4.6 pmol/L (2.3–12.0 pmol/L) in the unilateral group and 5.3 pmol/L (2.1–17.0 pmol/L) in the bilateral group (\( P = 0.36 \)). Seven patients in the unilateral group and 8 patients in the bilateral group had elevated serum PTH levels 5 years after surgery (\( P = 0.55 \)). Three of 15 patients with elevated serum PTH levels had persistent/recurrent pHPT. The remaining 12 patients had normal serum ionized calcium levels (range 1.15–1.27 mmol/L).

The follow-up rates were 97% (88 of 91) after 1 year and 78% (71 of 91) after 5 years. Of the 20 patients that were unavailable for 5-year follow-up, 16 had died and 4 refused further investigation. Two of these 20 patients had persistent pHPT. Two of the patients died within a year after surgery, thus no follow-up beyond 6 weeks was available. The remaining 16 patients had normal or slightly decreased serum ionized calcium levels at 1-year follow-up.

Thus, overall 6 patients of 91 included patients (6.6%) had persistent (\( n = 3 \)) or recurrent (\( n = 3 \)) pHPT; 4 patients in the unilateral group (3 of these 4 patients were bilaterally explored) and 2 patients in the bilateral group (Table 2). Two patients with recurrent disease were diagnosed at the one-year follow-up and 1 patient was diagnosed at the 5-year follow-up. The median age of the patients with persistent/recurrent pHPT was 62 years (range 33–84 years). All these patients had normal vitamin D status during follow-up. As seen in Table 2, the measurement of ioPTH 15 minutes after gland excision in the unilateral group predicted 2 of 4 failures in

### Table 1. Biochemical Data 1 Year and 5 Years after Surgery for Primary Hyperparathyroidism

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unilateral Group (n = 45)</th>
<th>Bilateral Group (n = 43)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum ionized calcium (mmol/L)</td>
<td>1.22</td>
<td>1.11–1.55</td>
<td>1.20</td>
</tr>
<tr>
<td>Serum PTH (pmol/L)</td>
<td>4.2</td>
<td>1.4–14.0</td>
<td>4.7</td>
</tr>
<tr>
<td>Serum phosphate (mmol/L)</td>
<td>1.04</td>
<td>0.69–1.39</td>
<td>1.09</td>
</tr>
<tr>
<td>Serum creatinine (μmol/L)</td>
<td>72</td>
<td>29–209</td>
<td>72</td>
</tr>
<tr>
<td>GFR (mL/min)</td>
<td>68</td>
<td>25–117</td>
<td>77</td>
</tr>
<tr>
<td>Serum alkaline phosphatase (μkat/L)</td>
<td>3.2</td>
<td>1.1–5.8</td>
<td>2.9</td>
</tr>
<tr>
<td>25 (OH) vitamin D₃ (nmol/L)</td>
<td>39</td>
<td>13–91</td>
<td>47</td>
</tr>
<tr>
<td>1.25 (OH)₂ vitamin D₃ (pmol/L)</td>
<td>47</td>
<td>19–240</td>
<td>52</td>
</tr>
<tr>
<td>1-Year Follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-Year Follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Data are not available for 5 years after surgery.

### Table 2. Patients With Persistent and Recurrent Hyperparathyroidism After Neck Surgery

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Randomized to Exploration</th>
<th>Identified Glands No.</th>
<th>Excised Glands No.</th>
<th>Pathology Report</th>
<th>Time to Recurrence</th>
<th>ioPTH Decline (%)</th>
<th>Serum Ionized Calcium Serum PTH</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Bilateral</td>
<td>Bilateral</td>
<td>4</td>
<td>1</td>
<td>Adenoma</td>
<td>&lt;6 wk</td>
<td>—</td>
</tr>
<tr>
<td>24</td>
<td>Unilateral</td>
<td>Bilateral</td>
<td>3</td>
<td>2</td>
<td>Hyperplasia</td>
<td>5 yr</td>
<td>62</td>
</tr>
<tr>
<td>38</td>
<td>Unilateral</td>
<td>Bilateral</td>
<td>3</td>
<td>1</td>
<td>Adenoma</td>
<td>&lt;6 wk</td>
<td>54</td>
</tr>
<tr>
<td>49</td>
<td>Unilateral</td>
<td>Bilateral</td>
<td>4</td>
<td>3.5</td>
<td>Normal</td>
<td>&lt;6 wk</td>
<td>16</td>
</tr>
<tr>
<td>78</td>
<td>Bilateral</td>
<td>Bilateral</td>
<td>4</td>
<td>2</td>
<td>Hyperplasia</td>
<td>1 yr</td>
<td>—</td>
</tr>
<tr>
<td>91</td>
<td>Unilateral</td>
<td>Unilateral</td>
<td>1</td>
<td>1</td>
<td>Adenoma</td>
<td>1 yr</td>
<td>76</td>
</tr>
</tbody>
</table>
this group, ie, a less than 60% decline in the PTH level. Thus 2 patients (patients 24 and 91) were ultimately, using a definition which is intended to determine the accuracy of ioPTH assessment in predicting long-term success, found to have false-positive ioPTH. Interestingly, these patients and another patient with recurrent pHPT in the bilateral group (patient 78) were unexpectedly (no family history and no clinical symptoms), found to have germline mutations in the genes for multiple endocrine neoplasia (MEN). Patient 24 and 91 had mutations in the MEND2 gene (RET proto-oncogene on chromosome 10), whereas patient 78 had a mutation in the MEN1 gene (MENIN gene on chromosome 11).

One patient with a solitary adenoma in the bilateral group still required vitamin D substitution 5 years after surgery. No other long-term complications were recorded.

**DISCUSSION**

The rate of parathyroid surgery seems to be increasing worldwide. Whether this increase reflects a true increase in the incidence of pHPT, a greater use of routine testing of serum calcium or an altered referral pattern for surgery is not known. In recent years minimal invasive and/or focused parathyroidectomy has challenged the traditional bilateral neck exploration for pHPT and it is suggested that part of the increase is related to the introduction of these less invasive techniques for parathyroid surgery. The new techniques are believed to have some distinct advantages over the conventional bilateral approach for the patient, for instance reduce the rate of early postoperative hypocalcemia, less postoperative pain and smaller scar, and thus there has been a global trend towards the acceptance among endocrine surgeons for these focused approaches. However, from a principle point of view, the main difference is between unilateral and bilateral neck exploration. The unilateral technique could be performed more or less invasive, open, or video-assisted, under local or general anesthesia. Furthermore, since in general, most focused techniques rely on ioPTH in contrast to the bilateral technique, which uses gross morphology and frozen section, these 2 approaches define a hyperfunctioning parathyroid gland differently, ie, a biochemical definition versus a gross morphologic definition. Interestingly, although several reports have demonstrated the feasibility of these less invasive procedures (open or video-assisted) as a treatment of pHPT, to date, there is only 6 randomized controlled trials with short-term results, including our study, published on the subject. In this context, it is important to stress the important difference between a feasibility study or case series and a prospective randomized trial. The latter, if well conducted, is assigned the highest level of evidence in evidence-based medicine.

The present study was the first unselected prospective randomized study analyzed on an intention-to-treat basis between unilateral and bilateral neck exploration. Randomization was done before sestamibi scintigraphy and scintigraphy was only performed in the unilateral group. This design of the study was used to avoid a selection bias, because it has been shown that patients with positive scintigraphy have a higher cure rate than patients with negative scintigraphy.

The previously presented results up to 6 weeks after surgery, showed that unilateral neck exploration offered some distinct benefits, especially for patients with solitary parathyroid adenoma, with lower incidence of biochemical and severe symptomatic hypocalcemia. Although the short-term results have been shown to be excellent, critics of limited parathyroid exploration have expressed concerns that enlarged potentially hyperfunctioning glands may be left in situ leading to a higher risk for long-term recurrent pHPT. This concern is mainly based on studies that have shown, during bilateral exploration, a number of patient with a remaining enlarged parathyroid gland after the hyperfunctioning gland had been excised (with a sufficient decline in ioPTH). However, since these glands also were excised during surgery it is not proved that these glands would have been hyperfunctioning if left in situ.

In the present study, we were able to demonstrate that unilateral neck exploration with intraoperative PTH assessment had the same long-term results as bilateral neck exploration. This is, to the best of our knowledge, the first open randomized trial of unilateral versus bilateral neck exploration for pHPT that presents long-term results (5-year follow-up). Russel et al have also shown in a randomized trial with a mean follow-up of 23 months that scan-directed unilateral cervical exploration does not significantly increase the incidence of postoperative hypercalcemia compared with conventional bilateral parathyroid surgery. However, their study population was selected since only patients with a positive sestamibi scan (1 residual focus of activity after subtraction) and a preoperative single tumor identified at the site suggested by the scan were included and preoperatively randomized to unilateral or bilateral exploration. Furthermore, they did not use ioPTH.

So far, the results of nonrandomized studies looking at patients undergoing parathyroid surgery in combination with ioPTH measurement have shown that a sufficient decline in ioPTH level is associated with excellent long term results (as long as 10 years after surgery). The results from the present study clearly make a further contribution to the evidence of a superb late outcome and support a biochemical definition of a hyperfunctioning parathyroid gland in sporadic pHPT.

There was no difference in cure rate or the rate of late hypocalcemia/hypoparathyroidism between the 2 groups. Interestingly, all 3 patients that developed recurrent pHPT were unexpectedly (no family history and no clinical symptoms) found to have germline mutations in MEN1 and MEN2 genes, respectively. We have previously described these patients and their mutations elsewhere. However, the only patient that required vitamin D substitution 5 years after surgery was a patient with solitary adenoma in the bilateral group.

In summary, unilateral neck exploration with ioPTH measurement is a valid surgical strategy with the same long-term results as bilateral exploration. Whether less invasive techniques can provide the same or even better results compared with sestamibi scan-directed unilateral “open”
REFERENCES


Discussions

Professor A. Frilling: Surgical treatment of primary hyperparathyroidism has changed significantly over the years and technetium-99m-sestamibi scintigraphy and intraoperative parathyroid hormone measurement have significantly contributed to this development. Minimally invasive surgery, whether directed or focused, presents the gold standard for surgical treatment. The contribution of the group from Lund to this field of surgery is well recognized and deserves our highest regard. The study presented here underscores the efficacy of minimally invasive parathyroid surgery and, most importantly, shows that the method is safe in terms of long-term results.

My questions are as follows: The failure rate was 8.5% and this seems to be higher than expected. However, 3 of your 6 patients in whom the disease recurred had MEN1 or MEN2. Since we know that hyperplasia, which is the normal finding in MEN patients, most often occurs in younger patients, what was the age of patients who had either persistent or recurrent disease? Were these individuals younger than the whole group of patients that you presented?

Second, in the group of unilaterally operated patients, there were those with the GFR fraction of 5 mL or 10 mL per minute. Could it be that some of these patients had secondary hyperparathyroidism? This could also contribute to the recurrence rate.

Third, I would like to focus again on the group of patients with persistent or recurrent disease. There was 1 patient in whom you identified all 4 glands, you removed 1 gland, which was an adenoma and the patient had recurrent disease. So, what was his problem? Did he have a second adenoma in an ectopic position or was one of the glands you primarily identified as normal, hyperplastic or a second adenoma? And, lastly, there was a patient in whom you identified all 4 glands. Three and one half were removed; the pathology report confirmed normal findings and this patient had a recurrence within 6 weeks after the operation. What was the problem in this patient?

Professor J. Westerdahl: Regarding the MEN1 and MEN2 patients, one might think that they would be the younger patients, but, actually, they were not. They were about the same age as all the other patients so that was really surprising. Even when we checked their history, we could not find any evidence of any sort of link to the MEN mutations.
As to your second question, you are right, some of the patients had some problem with renal function but we think they have PHPT and not secondary PHPT. Regarding your third question on the patient with 4 glands, we took out 1 gland and the histopathology said it was an adenoma but the patient had persistent disease. Actually, we do not know because the patient declined further investigations. As to your next question regarding the patient with 3.5 gland excision, this patient also refused further follow-up.

**Professor N. Senninger:** I completely agree with the concept you are suggesting and, yet, I think you have been a little bit unfair to the group of patients with bilateral exploration because they did not receive or were assessed by sestamibi scintigraphy. As far as I recall, you only did the scintigraphy with patients with unilateral exploration. Now, imagine you had done this with the bilateral group as well. If the 2 failures in the bilateral open group had been detected by the surgeon with the help of scintigraphy, resulting in zero operative failure, would your conclusion be somewhat different? The fact that you are dividing the patients into a unilateral group with everything that is available in modern medicine and a bilateral group with something that was available in the 1950s is what I mean by academically unfair.

**Professor J. Westerdahl:** I understand your question but we wanted to make a comparison with traditional bilateral exploration and, when you do that, you do not do any preoperative localization study.

**Professor N. Senninger:** Absolutely understood, but, if we exposed this protocol to our ethical committee and tell them that, for academic purposes, we are withholding the benefits of modern medicine from the patients with the bilateral exploration, they would not accept this study in Germany. I am 100% sure of that.

**Professor J. Westerdahl:** With the quality of our sestamibi scintigraphy, I am not sure that we would have localized these 2 patients with failures in the bilateral group. During this study, we calculated the sensitivity of sestamibi scintigraphy and it was only 71% during this study so I am not sure we would have found those glands.
Improved Kidney Graft Function After Preservation Using a Novel Hypothermic Machine Perfusion Device

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Objective: To study graft function and ischemia/reperfusion injury of porcine kidneys after preservation with the new Groningen Machine Perfusion (GMP) system versus static cold storage (CS).

Introduction: The increasing proportion of marginal and nonheart beating donors necessitates better preservation methods to maintain adequate graft viability. Hypothermic machine preservation (HMP) is a promising alternative to static CS. We have therefore developed and tested an HMP device, which is portable and actively oxygenates the perfusate via an oxygenator. The aim of the present study was to examine the efficacy of the GMP system in a transplantation experiment.

Materials and Methods: In a porcine autotransplantation model, kidneys were retrieved and either cold stored in University of Wisconsin CS for 20 hours at 4°C or subjected to HMP using University of Wisconsin machine perfusion at 4°C with 2 different pressure settings: 30/20 mm Hg or 60/40 mm Hg.

Results: HMP at 30/20 mm Hg was found to better preserve the viability of kidneys reflected by improved cortical microcirculation, less damage to the proximal tubule, less damage mediated by reactive oxygen species, less proinflammatory cytokine expression, and better functional recovery after transplantation. However, high perfusion pressures (60/40 mm Hg) resulted in higher expression of von Willebrand factor and monocyte chemotactic peptide-1 in post-preservation biopsies and subsequent graft thrombosis in 2 kidneys.

Conclusions: It is concluded that the GMP system improves kidney graft viability and perfusion pressures are critically important for outcome.


Maintaining organ viability between donation and transplantation is of critical importance for optimal graft function and survival. To date, static cold storage (CS) is the most widely practiced method in organ preservation. Although simple and effective, this method may no longer be sufficient to prevent further deterioration of the graft-to-be in an era with increasing numbers of older, more marginal, and even nonheart beating donors. An alternative method to maintain donor organ viability is hypothermic machine perfusion (HMP). HMP is, however, not a frequently used clinical preservation method. Based on data from the Organ Procurement and Transplantation Network ( OPTN) as of October 2006, only 20% of all kidneys are preserved using HMP in the United States. Although no accurate data are available, the numbers in Europe, by tradition, will be lower compared with the United States. In kidney preservation, both animal experiments and historical controlled clinical studies have demonstrated that HMP yields better early graft function compared with static CS.1,2 Most HMP devices in these studies, however, do not actively oxygenate the perfusate, which has been demonstrated to be an important additional feature of HMP by a number of groups.3,4 Also, and despite of the fact that HMP was introduced in the late sixties, uncertainty has remained about the optimal pressure settings, which vary per series between 30 and 60 mm Hg systolic, and 6 and 40 mm Hg diastolic.5–12 Although low pressure settings could underperfuse the kidney, especially the cortex, and lead to a higher delayed graft function, higher arterial pressures have been shown to enhance shear stress and damage the endothelium. To be able to clinically use HMP within an international organ sharing system, as in Europe, and still benefit from its advantages as described by Belzer and co-workers,13,14 we have developed a novel HMP device for kidney preservation. This compact, simple portable pulsatile hypothermic perfusion system incorporates advanced miniature technology and
Animals

• Group 2 with HMP 30/20 mm Hg, at 60 BPM (n = 5); Group 1 with CS (n = 5).

Experimental Design

The model used was a modification of a well-established porcine renal autotransplantation technique, which is a model for heart beating donation with minimal warm ischemia.1,15 Pigs underwent a left nephrectomy, after which this kidney was preserved for a period of 20 hours by either static CS or HMP using 2 different pressure settings. After preservation, the left kidney was autotransplanted and the right kidney was removed. Three experimental groups were studied:

• Group 1 with CS (n = 5);
• Group 2 with HMP 30/20 mm Hg, at 60 BPM (n = 5);
• Group 3 using HMP 60/40 mm Hg, at 60 BPM (n = 5).

Anesthetic Protocol

The anesthetic protocol was identical for nephrectomy and autotransplantation operations. Animals were premedicated with ketamine (10 mg/kg), xylazine (2 mg/kg), and atropine (10 μg/kg) intramuscularly. General anesthesia was induced with midazolam (0.3 mg/kg), pancuronium (0.15 mg/kg), and fentanyl (10 μg/kg) intravenously (IV). After endotracheal intubation using a 7-mm endotracheal tube, anesthesia was maintained with isoflurane 1% to 5% and oxygen was administered at 2 to 4 L/min. Animals were monitored intraoperatively by means of pulse oximetry using a tail probe.

Kidney Recovery and Storage

Surgery started with cannulation of the right internal jugular vein with a polyethylene (PE) catheter for infusion and collection of blood samples. Via a midline approach, a left nephrectomy was performed. The renal artery was cannulated immediately after procurement. Kidneys were flushed at a pressure of 100 cm H₂O (gravity) with 250 mL of University of Wisconsin cold storage solution (UW-CSS) at 4°C in the CS group or UW-machine perfusion solution at 4°C (UW-MPS) in the HMP groups.

GMP System

After flush out, HMP grafts were connected to the GMP system.16 This system consists of a disposable reservoir in which the kidney is placed (organ chamber), a miniature magnetic rotary pump (Deltastream DPII, MEDOS Medizintechnik AG, Stolberg, Germany) delivering pulsatile flow, a miniature hollow fiber membrane oxygenator (HILITE 800LT, MEDOS Medizintechnik AG, Stolberg, Germany), an oxygen cylinder, a battery pack, and a measurement and control unit that is connected to a palmtop computer (Fig. 1). The pulsatile pump directs the preservation solution (UW-MPS) from the organ chamber through the oxygenator and into the renal artery. Oxygen flow at 100 mL/Min resulted in a pO₂ > 100 kPa in the venous effluent. The pump is pressure-controlled, and recirculates the preservation solution with constant intrarenal perfusion pressures (30/20 or 60/40 mm Hg) at 60 BPM. Perfusion pressures were corrected for cannula resistance in each experiment. Perfusion flow rates were continuously monitored using clamp-on flow probes (H7C, Transonic Systems, Ithaca, NY). The GMP system is situated inside a standard polystyrene organ box (Wolters kunststoffen, Enter, The Netherlands), filled with melting ice to guarantee hypothermia for >24 hours.17

Renal Autotransplantation

After induction of general anesthesia the abdomen was reopened, the right kidney was removed and the graft was transplanted orthotopically. Before reperfusion, the graft was flushed with 250 mL of 0.9% NaCl at 4°C to wash out preservation solution. Vascular anastomoses were performed end-to-side (renal vein–vena cava) and end-to-end (left renal artery–right renal artery), respectively, using 6-0 polypropylene running sutures. The ureter was cannulated using PE tubing, which was subsequently tunnelled through the abdominal wall, allowing continuous visual inspection of urine formation. Reperfusion was established by release of the venous and arterial clamps, followed by infusion of 100 mL of 50% glucose to induce osmotic diuresis. Ten minutes after reperfusion, renal tissue perfusion was assessed noninvasively as mean erythrocyte flux, determined by Laser Doppler flowmetry (blood flow monitor DRT4, Moor Instruments, Axminster, England) as described in detail previously.4,18 To account for temporal variations in blood flow, we calculated the mean flux value over 10 seconds of recording, and to eliminate the influence of regional heterogeneity, measurements were performed at 3 distinct locations on the renal surface. All flux measurements were expressed as percent variation from the baseline value obtained from the nonischemic native kidney in each individual animal.

Postoperative Care

Free access to tap water was allowed immediately and supplemented with 2 L of 0.9% NaCl solution IV during the first 24 hours. Standard food was offered on the first postoperative day. Antithrombosis therapy was provided by 1 g of acetylsal-
icylic acid on a daily basis. Antibiotic treatment consisted of perioperative and subsequent administration of 500 mg of ampicillin IV on a daily basis. Venous blood samples were taken from the jugular catheter for measurement of renal function in terms of serum creatinine and electrolytes. The jugular catheter was flushed with heparin (3000 IU) after each sample. Daily urine output was measured and urine samples were taken. Animals showing any signs of distress or lethargy due to uremia were killed by lethal injection of T61 (Intervet, Munich, Germany) IV. Surviving animals were killed by injection of T61 on postoperative day 7, after removal of the transplanted graft under general anesthesia.

Tissue Preparation and Biochemical Analysis

Kidney Biopsies

Cortical renal biopsies were taken at different stages: before explantation (control), after preservation, before transplantation, and 10 minutes after reperfusion using a 14-gauge biopsy gun (ACECUT biopsy system, TSK Laboratory, Japan). The tissue specimen was subsequently halved and stored in 4% formalin or embedded (Tissue-Tek, Zoeterwoude, Netherlands) and snap frozen in isopentane at −80°C. Seven days posttransplantation of renal true cut tissue samples were obtained and stored in 4% formalin or snap frozen in isopentane at −80°C.

Microscopic Techniques

The collected tissue was paraffin embedded and cut into 4-μm-thick sections. Light microscopy (20× magnification) of hematoxylin and eosin and periodic acid-Schiff stained sections were used to demonstrate changes in morphology. Histology was reviewed using the modified ischemia reperfusion injury (IRI) scale. This scale quantitatively assesses the following items on a scale of 1 to 3 points (1, none; 2, medium; and 3, severe): mesangial matrix expansion, brush border loss in proximal tubule, edema, tubular dilatation, tubular cell vacuolisation, necrosis, endothelial cell swelling, and interstitial fibrosis. Points were added to create an IRI score (8–24 points). Biopsies of healthy pigs were used as reference. Immunohistochemical staining for von Willebrand factor (vWF) was performed as follows: incubation for 30 minutes in pepsin solution 0.2%, pH 2.0 at a temperature of 37°C. Primary antibody: polyclonal vWF 1:200 (Dako, Glostrup, Denmark), secondary antibody: GARPO 1:20 (Dako). The findings were graded semiquantitatively on a scale of 1 to 4 for the following features: vWF staining in glomerular endothelium, subendothelium, mesangium, and cortical vessels as previously described. The origin of all specimens remained blinded to the investigator during evaluation by light microscope.

Endothelial Activation and Inflammation

Real-Time Quantitative Taqman reverse transcriptase polymerase chain reaction (RT-PCR) analysis of vWF, monocyte chemotactic protein (MCP-1), E-Selectin and P-Selectin gene expression was performed to detect proinflammatory and/or procoagulatory activation, reflecting endothelial injury. All analyses were performed on tissue samples taken before and after preservation, 10 minutes after reperfusion and 7 days after transplantation. Total RNA was extracted from snap frozen tissue using TRIzol (Invitrogen, Breda, The Netherlands). Total RNA was treated with DNase I, Amp Grade (Invitrogen). First-strand cDNA synthesis, RT-PCR, and primer synthesis were essentially the same as described previously. All samples were assayed in triplicate. Results were normalized with the average value of the respective gene in control biopsies, arbitrarily set to 1.
Kidney Injury Biomarkers

Thiobarbituric acid reactive substances (TBARS) in urine were analyzed as an indication of increase in lipid peroxidation by reactive oxygen species (ROS) after reperfusion.22 Malondialdehyde binds to thiobarbituric acid and the subsequently formed TBARS were extracted in a butanol layer, measured with a fluorescence spectrophotometer at 485/590 nm (Baun de Ronde FL 600, Abcoude, The Netherlands). Urinary protein content was assayed via the method of Lowry et al.23 Activity of brush border enzymes alanine aminopeptidase (AAP) and lysosomal enzyme N-acetyl-β-D-glucosaminidase (NAG) in urine and perfusate were measured using colorimetric assays.24–26

Statistics

Data are expressed as mean ± standard error of mean (SEM). Statistical significance of differences was assessed using the Kruskal–Wallis test followed by a Mann–Whitney U test. P < 0.05 was considered statistical significant.

RESULTS

No significant differences in cold ischemic times (CIT) and anastomosis times were observed between groups. The mean (±SEM) CIT for the CS, HMP 30/20 and HMP 60/40 groups were 20:26 ± 0:16, 20:23 ± 0:13, and 20:26 ± 0:10 hours, respectively. The mean ± SEM anastomotic times were 32 ± 1, 30 ± 1, and 35 ± 1 minute, respectively. The first warm ischemia time (time between arterial clamping and cold flush out) ranged from 2 to 6 minutes and did not differ significantly between groups. In both, CS and HMP 30/20 groups all animals survived the 7-day follow-up period. In contrast, only 3 of 5 animals survived in the HMP 60/40 group. Both deaths were due to renal transplant failure.

Perfusion Dynamics

Renal artery flow measurements during HMP showed a significant increase in flow, from 38 ± 2 mL/Min initial to 65 ± 4 mL/Min after 20 hours in the HMP 30/20 group. This indicates a reduction of vascular resistance over time. In the HMP 60/40 group, a similar pattern was observed with an initial flow of 49 ± 7 mL/Min rising to 104 ± 10 mL/Min at 20 hours. Continuous temperature registration showed a stabilization of graft core temperature at 2°C to 4°C after 2 hours of HMP in both groups.

Reperfusion Injury

ROS Formation

Measurement of TBARS in urine produced immediately after reperfusion allowed detection of ROS production. TBARS levels in urine from CS grafts were significantly higher compared with HMP 30/20 and HMP 60/40 groups. Urinary TBARS after CS were 21.9 ± 2.2 mmol/L compared with 9.8 ± 1.2 and 10.3 ± 1.8 mmol/L, respectively, after HMP 30/20 and HMP 60/40 (Fig. 2).

Proximal Tubule Damage

Detection of NAG and AAP activity in urine allowed an assessment of injury to the proximal tubule immediately after reperfusion. Urine concentrations of NAG were significantly higher in urine from CS grafts compared with both HMP groups. Urinary NAG concentrations were 84.2 ± 27.1 U/L after CS compared with 8.5 ± 1.7 U/L after HMP 30/20 and 8.9 ± 2.3 U/L after HMP 60/40. The results with AAP and proteinuria showed a similar pattern (Fig. 2).

Microcirculation

Microcirculatory tissue perfusion of the renal cortex 10 minutes after reperfusion showed significant differences between groups. Cortical erythrocyte flux was significantly higher in both HMP groups, averaging 130% ± 10% (HMP 30/20) and 109% ± 4% (HMP 60/40) of controls compared with 85% ± 8% in CS grafts (P < 0.05).

Renal Histology

The modified IRI score did not differ significantly between groups. Overall, low scores (maximum 12/24) were observed. Although a moderate increase of damage was seen over time, this did not reach statistical significance.

Endothelial Activation and Inflammation

Three endothelial injury markers and 1 proinflammatory cytokine were studied to examine the influence of CS and HMP on endothelial cell activation and inflammation. Biopsies were taken at 4 time points: before and after preservation, after reperfusion, and at autopsy. In kidney grafts preserved with HMP 30/20, vWF mRNA expression in the postpreservation biopsy was similar to CS. An almost 2-fold increase in vWF mRNA expression was, however, seen in HMP 60/40 preserved kidneys compared with CS grafts (P < 0.05). These findings were confirmed with immunohistochemical staining showing increased vWF staining in HMP 60/40 (3.75 ± 0.25) grafts compared with CS (0.8 ± 0.5) and HMP 30/20 (0.6 ± 0.25; P < 0.05; Fig. 3). Furthermore, HMP 30/20 preserved kidneys showed a significant lower expression of MCP-1 compared with HMP 60/40 in the postpreservation biopsy (P < 0.05, Fig. 4). In contrast to vWF and MCP-1 expressions, E-Selectin and P-Selectin mRNA expressions did not differ significantly between groups.

Renal Function

Posttransplant renal function data are presented in Figure 5. Preservation by HMP resulted in a significant improvement renal function after transplantation. Peak serum creatinine levels and time to peak serum creatinine were significantly lower in both HMP groups. Animals with transplanted kidney grafts after CS preservation showed a peak serum creatinine of 940 ± 90 μmol/L on postoperative day 3.4 ± 0.89. In contrast, animals that received HMP 30/20 kidneys had a significantly lower peak creatinine of 463 ± 127 μmol/L on postoperative day 1.8 ± 1.1. Surviving pigs in the HMP 60/40 group showed similar results to HMP 30/20 animals with a peak creatinine of 428 ± 129 μmol/L on postoperative day 1.7 ± 0.6. However, only 3 animals survived with adequate renal function in this group. The autopsy on 2 animals with renal failure, as demonstrated by rising creatinine levels, revealed diffusely black colored grafts with open arterial and venous anastomoses.
DISCUSSION

Because many centers, due to the persistent donor shortage, will accept older, more marginal, and even nonheart beating donors, conventional static CS might not be sufficient anymore to maintain organ viability during preservation. This study demonstrates that HMP at a pressure of 30/20 mm Hg using the portable GMP system with pulsatile perfusion and oxygenation improves 20 hours cold preservation of porcine kidneys. In the past, several experimental studies have addressed the role of machine perfusion in renal preservation using large animal models. Most studies available, however, are small and have used canine kidneys, which are in contrast to human, relatively resistant to cold ischemic injury. The porcine kidney seems to be more sensitive to cold preserv-
tion as demonstrated by Nicholson et al.1 For this reason, we have limited CIT to 20 hours in our model. The pig was also chosen as an experimental model, because its renal anatomy and physiology resemble the human situation.1,28,29 An autotransplant model was used to rule out allogeneic immune responses allowing unbiased investigation of ischemia and reperfusion injury. To determine renal function of the autotransplanted kidney a simultaneous contralateral nephrectomy was performed. CS preservation was chosen as a control, because 80% of all kidneys is still preserved using CS (OPTN data, October 2006). The rationale for the preservation solutions used was as follows. UW-CSS and UW-MPS are similar solutions. UW-CSS contains lactobionate versus gluconate as an impermeant and has an intracellular instead of an extracellular sodium/potassium ratio. UW-CSS is at present considered to be the “gold standard” solution for static CS. In a direct comparison in the CS setting, UW-lactobionate (UW-CSS) was found to have a slightly better composition for suppression of hypothermia induced cell swelling compared with UW-gluconate (UW-MPS).30 For this reason, we used UW-CSS in the control group.

In the HMP 30/20 group, 5 of 5 animals survived. Recovery of renal function was significantly improved compared with the CS group, with an approximate 50% reduction of peak creatinine and time to reach this maximum creatinine. As mentioned earlier, this improvement of posttransplantation viability cannot be explained by the small differences between the solutions. Compared with the study of Nicholson, values obtained in the present experiment are better, which can be explained either by the shorter CIT, ie, 20 hours versus 24 hours, or the use of the GMP system instead of the Waters HMP system.1 Moreover, we could demonstrate improved microvascular tissue perfusion upon reperfusion after HMP, whereas the lower erythrocyte flux in the CS groups indicated a reduced vascular viability of these grafts. This finding is in line with previous observations that high oxygen availability during preservation improves microcirculatory parameters.4 The use of oxygen, in the GMP system, with a venous \( pO_2 > 100 \) kPa may be especially beneficial for endothelial cells, because these cells are critically sensitive to anoxia that leads to endothelial cell swelling and the so-called “no-reflow” phenomenon. This effect may account for the impaired vascular performance of CS grafts.31–33

Another beneficial effect of active oxygenation during preservation was seen in reduced ROS formation after reperfusion in both HMP groups. This is in accordance with earlier findings in rodent models.3,34–36 In addition to the reduced level of toxic ROS formation, less urinary release of proximal tubule injury markers AAP and NAG was observed after reperfusion of especially the HMP 30/20 preserved grafts compared with CS. Both enzymes were not detectable in UW-MPS (data not shown), thus demonstrating that the enzymes had not been already washed out during perfusion preservation. Many studies have pinpointed the damage to tubular cells as an important risk factor for the presence of delayed graft function.37 The fact that proximal tubules were less injured in the HMP 30/20 group could very well explain the earlier and better functional recovery of kidneys preserved by HMP.

A potential negative effect of HMP, in general, could be the occurrence of vascular injury due to shear stress.39–40 Shear stress is a parallel frictional drag force that is linearly proportional to the flow and the viscosity of the fluid.41 Obviously, shear stress can easily negatively affect the integrity of vascular endothelial cells and cause cellular detachment. In this study, pulsatile pressures of 30/20 and 60/40...
mm Hg were applied at 60 BPM during 20 hours HMP. We could not demonstrate any significant differences between surviving animals in these groups in terms of morphology, quantified using the modified ischemia-reperfusion-injury scale. Renal function of surviving 60/40 animals was comparable with 30/20 grafts. Quantitative RT-PCR analysis and immunohistochemical staining revealed, however, a higher expression and staining of vWF mRNA in biopsies after preservation in the HMP 60/40 group compared with CS. The release of vWF is regarded as an important marker of endothelial cell disturbance. Perturbation of endothelial cells during HMP can indeed stimulate the synthesis of vWF. Platelets will subsequently adhere to vWF and initiate thrombus formation. This cascade might explain the observation of a more bluish aspect during reperfusion of HMP 60/40 grafts compared with CS and HMP 30/20 groups. Furthermore, the higher vWF synthesis might also explain the lower microcirculation in the HMP 60/40 group compared with HMP 30/20. More importantly, a marked difference in survival was seen: in the HMP 60/40 group 2 animals died of renal failure versus none in the other groups. At autopsy black grafts were observed without any evidence for technical failure, eg, arterial or venous anastomotic occlusion or complications. This observation suggests diffuse vascular damage, presumably secondary to overexpression and synthesis of vWF during HMP at 60/40 mm Hg because of higher shear rates. Thus, pulsatile pressure of 60/40 mm Hg using UW-MPS might damage the endothelial cells during HMP in porcine kidneys. There are some studies from the early seventies showing a relationship between perfusion pressure and endothelial damage. These studies, however, were performed with different perfusates and using rabbit or canine kidneys. The conclusion of these early experiments was to use a low systolic pressure of approximately 40 mm Hg. Despite these studies, however, 60 mm Hg systolic pressure is still common clinical practice in human kidney preservation. The present study, again, underscores the importance of perfusion pressures. Although our numbers are small and porcine kidneys are possibly more susceptible to endothelial injury, this primarily indicates that perfusion settings in human kidneys ought to be reconsidered and may be lowered.

To study the immunogenicity of the graft following preservation, we measured the expression of the proinflammatory chemotactic cytokine MCP-1. This cytokine is important in neutrophil dependent injury and is expressed by a variety of cells including vascular endothelial cells. HMP 30/20 showed the lowest expression of MCP-1. Several experimental models have shown upregulation of proinflammatory cytokines and selectins in kidney grafts during cold ischemia. We postulate that oxygenation during preservation at low shear rates minimizes proinflammatory cytokine expression. Similarly, in a rat liver model of oxygenated machine perfusion a marked lower expression of intracellular adhesion molecule-1 was found in HMP grafts compared with CS. The higher expression of MCP-1 in the HMP 60/40 group is most probably due to shear stress, which is also reflected in the higher expression and synthesis of vWF in this group.

The portable GMP uses simple but new miniature technology that will fit in the conventional organ box as currently used in transplantation. Special features include back-up with CS in case of total power failure and an option of normothermic perfusion by using a heat exchanger and blood compatible disposable components. The total added weight of the prototype compared with CS concerns only 4.8 kg.

In summary, this study demonstrates that the GMP system using pulsatile oxygenated perfusion of 30/20 mm Hg at 60 BPM allows kidney preservation for 20 hours in a pressure-controlled manner. More importantly, the GMP system improved posttransplant kidney function of heart beating porcine kidneys compared with standard static CS with UW-CSS. Preset perfusion pressures, however, are found to be critically important for successful outcome after HMP. Too high perfusion pressures during HMP provoke an inflammatory response, harm the endothelium and can cause subsequent diffuse thrombosis of the graft. In contrast, if a pressure of 30/20 mm Hg during HMP is applied: less toxic ROS are generated, less injury to the proximal tubule occurs, less proinflammatory cytokines are expressed, and the cortical microcirculation is improved. As we have now shown the practical feasibility of the GMP system, future studies will focus on its application in nonheart beating donors and on a clinical comparison with other portable HMP devices.

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metabolites? People have considered these 2 issues but there is no solid evidence either way at this stage.

The second issue I would like to address is one of pressure. Clearly, what you demonstrated is that pressure matters and that lower pressure is better than higher pressure. How did you establish which 2 pressures to study? Was it on the basis of prior studies looking at oxygen consumption or looking at microperfusion and do you think this is species-specific? I think what you demonstrated is that hypothermic machine perfusion is clearly highly nonphysiological, because at rather low pressures you are managing to achieve quite high levels of vascular endothelial damage.

The next issue is that of the immunohistochemical markers of injury. What is very interesting is that, despite the marked functional differences between the cold-stored and the machine-perfused groups, you have not, in fact, demonstrated important differences in ischemia reperfusion index or in expression of P-selectin or E-selectin and so the question really is; what is the mechanism of injury that you avoid with machine perfusion?

Next, expressing my own bias on this matter, if you are going to deliver oxygen you should deliver it at a higher temperature because the main advantage of low temperature is that you are reducing cellular metabolism. If you are providing oxygen, then it seems to me that you do not need to reduce cellular metabolism in the same way. Why not warm it up, which is clearly what you are doing with your colleagues in Barcelona and, if so, what do you think the optimum pressure might be?

Finally, in what way do you think that your results from these pristine porcine kidneys will translate to marginal kidneys that have sustained significant preretrieval damage?

DR. M.-H. MAATHUIS: As to your first question regarding the actual principle of HMP, in my opinion there are 3 beneficial components in HMP. Firstly, there is the mechanical effect of a prolonged and better washout of blood and removal of waste products. Furthermore, there is a biochemical effect of a deeper and better tissue penetration of the preservation solution. And finally, especially when you add oxygen, there is a metabolic support effect because, even at these low temperatures, there is still 10% to 12% metabolism taking place.

Your second question concerns our pressure settings during HMP. A colleague of mine, Nils ’t Hart, did previous rat experiments where he showed that 30/20 mm Hg was optimal in rats. So that is why we included this pressure group. However, especially in US centers, 60/40 mm Hg is often used clinically, and that is why we included this higher pressure group and compared it to the laboratory settings.

As to your third question regarding the mechanism of injury, by adding oxygen I think we avoid the metabolic derangement of the organ during hypothermia. Apparently, this does not result in changes in histology but based on functional parameters we can see an improvement of organ viability, leading to improved organ function.

Regarding your fourth question about oxygen and metabolic support, I agree with you that raising the temperature does probably lead to better preservation because you avoid the damaging effect of hypothermia. However, it is especially difficult in the clinical setting to include this more complex system in everyday transplantation medicine. This will be the focus of our research in the next 10 years.

In answer to your last question, how do these results translate to marginal organs? We are planning experiments in a nonheart-beating setting. In fact, in the liver experiments in Barcelona, we apply 90 minutes of warm ischemia. There, we compare cold storage with HMP and NMP and, again, we see an improved viability when comparing HMP with cold storage. The pig kidney is very sensitive to cold ischemia. It is more sensitive than the human kidney and much more sensitive than the dog kidney, which we used years ago. So I think that the differences that we see here will apply for marginal organs as well.

PROFESSOR P.-A. CLAVIEN: We all realize that this is the achievement of many years of hard work in attempting to ameliorate organ preservation through machine perfusion. To be clinically applicable, machine perfusion must be easy to handle, easily transportable from the site of harvesting to the transplant center, and effective. Although kidneys are small and, contrarily to the liver, have a single perfusion system, they are often harvested by other surgeons, other than those belonging to the kidney transplant team, who may not be familiar with perfusion machines. Last year, we presented a similar device for hypothermic oxygenation perfusion (HOPE) of cold preserved livers at the ESA meeting, but the machine was merely plugged in for 1 hour before implantation. This “rescue” approach is very effective and has the advantage of being used only at the transplant center. My question is did you try a similar strategy; for example, by subjecting a kidney to a long cold (brain dead donor situation) or warm + cold ischemia (nonheart-beating situation), and then use your system for a short period before implantation in an attempt to rescue the kidney graft?

DR. M.-H. MAATHUIS: I agree that HMP is more complex than static cold storage and I have read your article concerning the HOPE system where you perform HMP after static cold storage right before implantation. I think we should test it with this system as well, which we have not done so far. One down side of this strategy may be that most of the damage is in the beginning of preservation when temperatures are still high. Metabolic support at this point could result in improvement of viability but, as I said, we should test the application of HMP with this system following static cold storage.
PROFESSOR T. VAN GULIK: It is good that you emphasize the need to focus more on preservation methods to improve the quality of organ grafts. My first question relates to your set-up in which you tested the noncompromised kidneys in the cold storage setting and in the machine perfusion setting. To my mind, the creatinine values in the cold storage group are quite high. Maybe you can comment on how that relates to the literature and if they were exceptionally high in your cold storage group?

You stressed the importance of oxygenating your organ and we all know that, although the temperature is 4°C, there is a level of metabolism going on that you need to support. My second question is, how do you know that the oxygen you deliver is actually reaching the cells because you are delivering oxygen as a kind of persufflation. When you persufflate fluid medium, the concentration in the fluid is not as high as you might expect. So, my question is, did you actually measure oxygen tension in your medium. You would probably have to conduct some oxygen consumption tests to see if it really has the effect you expect.

My last question is about the perfusion fluid you have been using. Your last slide suggested that it would be a blood-containing perfusion solution because it was all red. Of course, there is a big difference if you have an oxygen carrier in your perfusion fluid then you are sure that you are delivering your oxygen in the optimal way.

My question is what kind of perfusate did you use? Did you use the UW gluconate modification or was it some other kind of perfusate.

DR. M.-H. MAATHUIS: Concerning the set-up and the literature about the cold storage creatinine levels in pigs, several other reports show more or less the same profile with high creatinine levels. There is a publication by Nicholson in Transplantation in 2004 showing exactly the same curves. In conclusion, we have not done anything wrong, but the pig is just a very sensitive model that results in more kidney damage, even with a short amount of CIT.

As to the question about oxygen, Nils ’t Hart has done a lot of basic laboratory work on the prototype of this machine. He demonstrated, in isolated perfused organ settings, that the oxygen we add to the UW-MP solution does reach the cells and does lead to increased ATP levels and increased synthesis function of these cells. Although it is not as adequate as you would find with an oxygen carrier, there is still sufficient oxygen delivery to the cells.

The solution we used was, indeed, UW-MP and my last slide referred to the experiments we are currently conducting in Barcelona, where we use a blood based perfusate for normothermic machine perfusion. The reason we use UW-MP for hypothermic machine perfusion is because it is the only clinically registered solution for HMP.
Extended Transthoracic Resection Compared With Limited Transhiatal Resection for Adenocarcinoma of the Mid/Distal Esophagus

Five-Year Survival of a Randomized Clinical Trial

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Objective: To determine whether extended transthoracic esophagectomy for adenocarcinoma of the mid/distal esophagus improves long-term survival.

Background: A randomized trial was performed to compare surgical techniques. Complete 5-year survival data are now available.

Methods: A total of 220 patients with adenocarcinoma of the distal esophagus (type I) or gastric cardia involving the distal esophagus (type II) were randomly assigned to limited transhiatal esophagectomy or to extended transthoracic esophagectomy with en bloc lymphadenectomy. Patients with peroperatively irresectable/incurable cancer were excluded from this analysis (n = 15). A total of 95 patients underwent transhiatal esophagectomy and 110 patients underwent transthoracic esophagectomy.

Results: After transhiatal and transthoracic resection, 5-year survival was 34% and 36%, respectively (P = 0.71, per protocol analysis). In a subgroup analysis, based on the location of the primary tumor according to the resection specimen, no overall survival benefit for either surgical approach was seen in 115 patients with a type II tumor (P = 0.81). In 90 patients with a type I tumor, a survival benefit of 14% was seen with the transthoracic approach (51% vs. 37%, P = 0.33). There was evidence that the treatment effect differed depending on the number of positive lymph nodes in the resection specimen (test for interaction P = 0.06). In patients (n = 55) without positive nodes locoregional disease-free survival after transhiatal esophagectomy was comparable to that after transthoracic esophagectomy (86% and 89%, respectively). The same was true for patients (n = 46) with more than 8 positive nodes (0% in both groups). Patients (n = 104) with 1 to 8 positive lymph nodes in the resection specimen showed a 5-year locoregional disease-free survival advantage if operated via the transthoracic route (23% vs. 64%, P = 0.02).

Conclusion: There is no significant overall survival benefit for either approach. However, compared with limited transhiatal resection extended transthoracic esophagectomy for type I esophageal adenocarcinoma shows an ongoing trend towards better 5-year survival. Moreover, patients with a limited number of positive lymph nodes in the resection specimen seem to benefit from an extended transthoracic esophagectomy.


The incidence of adenocarcinoma of the esophagus and gastroesophageal junction is rapidly rising. It is an aggressive disease with early lymphatic and hematogenous dissemination. Long-term survival rates barely exceed 25%, even after surgery with curative intent.1,2 Surgery is still considered the best curative treatment option. However, much controversy concerning the optimal surgical approach exists.

Two main operation techniques are currently advocated. Limited transhiatal esophagectomy (THE) (without formal lymphadenectomy) aims at decreasing early postoperative morbidity and mortality. Whereas extended transthoracic esophagectomy (TTE) with en bloc lymphadenectomy is intended to improve long-term survival by performing a combined (cervico) thoracoabdominal resection, with wide excision of the tumor and peritumoral tissues and extended lymph node dissection in the posterior mediastinum and upper abdomen.
Worldwide, only 4 randomized studies have been performed to compare these 2 approaches.\textsuperscript{3–6} In these studies, with exception of the study performed by our group,\textsuperscript{5} no statistically significant differences were found in morbidity and in (short-medium term) survival between both techniques. Our group reported that a THE was associated with a significantly lower morbidity, while there was a trend towards improved medium-term survival with the extended approach.\textsuperscript{5}

We present the complete 5-year survival data after limited transhiatal versus extended TTE to assess the overall value of both techniques.

**PATIENTS AND METHODS**

**Study Design**

The study was performed in 2 academic medical centers, each performing more than 50 esophagectomy procedures per year. The eligible patients had histologically confirmed adenocarcinoma of the midto-distal esophagus or adenocarcinoma of the gastric cardia substantially involving the distal esophagus, did not show evidence of distant metastases (including the absence of cytologically confirmed tumor-positive cervical lymph nodes and irresectable celiac lymph nodes), and did not have irresectable local disease. These patients were randomly assigned to undergo THE or TTE with extended en bloc lymphadenectomy between April 1994 and February 2000.

Patients had to be older than 18 years of age and in adequate physical condition to undergo major surgery (as indicated by their assignment to American Society of Anesthesiologists class I or II\textsuperscript{1}). Exclusion criteria were previous or coexisting cancer, previous gastric or esophageal surgery, application of neoadjuvant chemotherapy and/or radiation therapy, and distal extension of the tumor that made it impossible for the surgeon to construct a gastric tube. The preoperative diagnostic work-up consisted of endoscopy with biopsy and histologic examination, endosonography, external ultrasonography of the abdomen and neck (with biopsy if indicated), chest radiography, indirect laryngoscopy, and bronchoscopy if tumor ingrowth in the upper airway was suspected. Computed tomography (CT-scan) was performed only when indicated. Although CT-scanning was introduced as an integrated part of the preoperative work-up during the second part of the study period in both academic institutes, it was decided not to include CT-scanning in the study protocol during the second part because it was believed to cause imbalance between and within the randomized groups. Patients with carcinoma of the cardia underwent laparoscopy with laparoscopic ultrasonography. Positron emission tomography (PET) was not performed. After written informed consent was obtained, the patients were randomly assigned to 1 of the 2 surgical procedures 2 to 4 weeks before surgery. Randomization was stratified according to the hospital and tumor site (esophagus or cardia, as indicated by endoscopy). No blocking was used within each of the 4 strata.

**Surgery and Pathologic Examination**

Surgery was performed by or under direct supervision of a surgeon-investigator with large experience in esophageal surgery. During THE, the esophagus was dissected under direct vision through the widened hiatus of the diaphragm, at least up to the inferior pulmonary vein. The tumor and its adjacent lymph nodes were dissected en bloc. A 3-cm-wide gastric tube was constructed. The left gastric artery was transected at its origin, with resection of local lymph nodes. Celiac lymph nodes were dissected only when there was clinical suspicion of involvement. After right-sided mobilization of the cervical esophagus, the intrathoracic, normal esophagus was bluntly resected from the neck to the abdomen with use of a vein stripper. Esophagogastrectomy was performed in the neck, without cervical lymphadenectomy. Posterolateral thoracotomy was the first step in transthoracic resection with extended en bloc lymphadenectomy. The thoracic duct,azygos vein, ipsilateral pleura, and all periesophageal tissue in the posterior mediastinum were dissected en bloc. The specimen included the lower and middle mediastinal, subcarinal, and right-sided paratracheal lymph nodes (dissected en bloc). The aortapulmonary-window nodes were dissected separately. Through a midline laparotomy, the paracardial, lesser curvature, left-gastric-artery (along with lesser curvature), celiac trunk, common-hepatic-artery, and splenic-artery nodes were dissected, and a gastric tube was constructed. The cervical phase of the transthoracic procedure was identical to the transhiatal procedure, but a left-sided approach was used.\textsuperscript{8} In both procedures, the origin of the left gastric artery was marked. Subcarinal nodes were marked separately in case of a planned transthoracic resection. The resection specimen was carefully palpated for the presence of lymph nodes and subsequently dissected. All lymph nodes identified by the pathologist were collected in separate boxes and marked according to location, then cut into 2 with both sides stained with hematoxylin and eosin. Pathologic grading was performed by or under supervision of an investigator who was a senior gastrointestinal pathologist. Tumors were assigned pathologic tumor-node-metastasis stages according to the Union Internationale Contre le Cancer 1997 system. With respect to staging, carcinoma of the cardia and distal esophageal carcinoma were considered a single clinical entity.\textsuperscript{9–11} Early postoperative complications were prospectively scored by the study coordinators. Epidural analgesia was used postoperatively to minimize pulmonary complications.

**Follow-up and Assessment of End Points**

None of the patients received adjuvant chemo- and/or radiation therapy after the operation. All patients were seen at the outpatient clinic at intervals of 3 to 4 months during the first 2 years and every 6 months for 3 more years. After 5 years, follow-up data were obtained by telephone from the patient or his/her family practitioner. Recurrence of disease was diagnosed on clinical grounds. However, whenever a relapse was suspected, radiologic, endoscopic, or histologic confirmation was sought. Recurrent disease was classified as locoregional (occurring in the upper abdomen or mediastinum) or distant (including cervical recurrences). Overall
survival and disease-free survival were the main end points of the study. Because the aim of an extended resection is to gain more locoregional control, locoregional disease-free survival was also an end point of this study.

**Statistical Analysis**

SPSS 12.0.1 for Windows and SAS version 9.1 were used for statistical analysis. Survival times were calculated from the time of randomization to death from any cause or the time to the last follow-up visit (at which time data were censored). Disease-free survival was counted up to the time of a first relapse and patients were censored at the time of their last visit or when they died of nondisease-related causes without a previous relapse. Survival curves were constructed by the Kaplan–Meier method, and the log-rank test was used to determine significance.

For subgroup analysis, patients were divided by the location of the primary tumor12 and by the number of positive lymph nodes (percentiles; 0%–25%, 25%–75%, 75%–100%). Conceptually, a patient without positive lymph nodes will not benefit from a more extended lymph node dissection. Therefore, a subgroup was chosen of N0 patients. Since this happened to be approximately one quarter of the patients, also one quarter of the patients with multiple positive nodes was taken to represent the subgroup at the other end of the spectrum. For these purposes, the pathologic examination of the resection specimen (and not the preoperative endoscopic assessment) was considered the gold standard.

The following approach was used to perform a formal test of interaction to determine whether the size of treatment effect differed between subgroups. Within a Cox regression model, survival was modeled as a function of trial treatment (categorical with 2 levels), the variable holding the subgroup either location (categorical with 2 levels) or number of positive lymph nodes (categorical with 3 levels) and the interaction term between trial treatment and the subgroup variable. The P value associated with the test whether the coefficient of the interaction term is zero was used as the formal test of interaction.13 All reported P-values are twosided. P-values below 0.05 were considered to indicate statistical significance.

**RESULTS**

A total of 220 patients with adenocarcinoma of the distal esophagus (type I) or gastric cardia substantially involving the distal esophagus (type II) were randomly assigned to limited THE or to extended TTE with en bloc lymphadenectomy. The overall survival of all randomized patients (n = 220) on the intention to treat basis is shown in Figure 1.

Based on the preoperative endoscopic examination, 180 patients were classified as having a type I tumor and 40 patients as having a type II tumor. In 3 patients who were allotted to a transthoracic resection it was decided to perform a total gastrectomy because the tumor appeared to be limited to the proximal part of the stomach. One patient did not undergo resection because of massive aspiration. The presence of unresectable local tumor, distant metastases, or both (detected early during operation) precluded resection in 11 patients.

These 15 patients in total were excluded from further analysis. Patients who died in the hospital and patients with R1–2 resections were included in the present analysis because all patients were operated on with curative intent. The clinicopathological characteristics of the 205 remaining patients are summarized in Table 1 and were comparable for both groups. Follow-up was complete in all patients. In all patients, the operation was performed at least 5 years earlier, ensuring a minimal potential follow-up of 5 years (range 5–10.6 years). During follow-up, 139 patients (68%) had deceased; 6 patients (3%) died in-hospital because of postoperative complications, 118 patients (58%) died with recurrent disease, whereas 15 patients (7%) died of an unrelated cause (Table 2). Overall 5-year survival was comparable between patients after transhiatal resection (34%) and patients after transthoracic resection (36%, P = 0.71) (Fig. 2).

Subsequently, patients were subdivided by location of the primary tumor (type I: esophageal vs. type II: cardia). Based on the postoperative pathologic examination of the resection specimen (gold standard), 90 patients (43 patients in the transhiatal group and 47 patients in the transthoracic group) were classified as having a type I tumor, whereas 115 patients (52 patients in the transhiatal group and 63 patients in the transthoracic group) were classified as having a type II tumor (Table 1). For patients with esophageal cancer (type I), transthoracic resection resulted in a 14% (95% confidence interval for the difference −6% to 34%) 5-year survival benefit (37% after THE vs. 51% after TTE) (Figs. 3 and 4A). For patients with cardiac cancer (type II), the 5-year survival difference was negligible (31% after THE vs. 27% after TTE; 5-year survival difference −4%, 95% confidence interval for the difference −13% to 21%) (Figs. 3 and 4B).

Patients were also subdivided by the number of positive lymph nodes in the resection specimen (Table 1). In patients
without positive lymph nodes, locoregional recurrence occurred in 11% of patients operated via the transhiatal approach and in 7% of patients operated via the transthoracic approach, resulting in a 5-year locoregional disease-free survival of 86% and 89%, respectively (Figs. 3 and 5A). Patients with more than 8 positive lymph nodes showed 33% locoregional recurrence in the transhiatal group and 45% in the transthoracic group, resulting in no locoregional disease-free survival advantage for either approach (Figs. 3 and 5C). However, patients with 1 to 8 positive lymph nodes in the resection specimen showed an overall survival difference of 20% if operated on via the transthoracic approach (19% after THE vs. 39% after TTE; 95% confidence interval for the difference 3% to 37%, \( P = 0.05 \)). Moreover, locoregional recurrence occurred in 42% of patients operated via the transhiatal approach and in 25% of patients operated via the transthoracic approach, resulting in a 5-year locoregional disease-free survival advantage if operated via the extended transthoracic procedure (23% after THE vs. 64% after TTE; 5-year survival difference 41%, 95% confidence interval for the difference 24% to 58%, \( P = 0.02 \)) (Figs. 3, 5B, and 6). Strikingly, only 11 of the 26 patients (42%) with a type II tumor and a limited number (N 1–8) of positive lymph nodes developed a locoregional recurrence after transhiatal resection.

### DISCUSSION

In this final analysis, we demonstrate that there is no significant overall survival benefit for either approach, although the previously reported trend towards better survival after extended resection persists during long-term follow-up.\(^5\) In this study, both patients with adenocarcinoma of the mid to distal esophagus (type I) and patients with adenocarcinoma of the gastric cardia substantially involving the distal esophagus (type II) were included. Although these 2 tumor types are considered 1 clinical entity by some authors,\(^1\) many discrepancies exist in the literature regarding the etiology and classification of these tumors.\(^14\) For this reason, different surgical approaches are recommended with different survival rates reported in the literature.\(^10\)–\(^12\) In the present study, a subgroup analysis was performed based on the location of the tumor (esophageal type I vs. cardiac type II)\(^12\) according to the pathology report of the resection specimen. Patients with type I esophageal cancer had a 14% (95% confidence interval for the difference 24% to 34%) overall 5-year survival benefit if operated via the extended transthoracic approach. For patients with type II cardiac carcinoma, no overall survival benefit was seen for either approach, and for these patients, an extended lymph node dissection is definitely not useful. These findings are in line with those recently published by Sasako et al.\(^15\) In a randomized trial, they compared the extended left thoracoabdominal approach with the limited transhiatal approach for cancer of the cardia or subcardia (types II and III)\(^15\). Also in that study, no survival difference was found for type II carcinomas with either approach.

It should be notified that a substantial difference existed between the endoscopic tumor classification, which was used for the preoperative stratification process, and the pathologic tumor classification in the resection specimen (gold standard), which was used in this subgroup analysis. Apparently the endoscopists in the 2 participating hospitals tended to classify tumors at the gastroesophageal junction as type I.

### TABLE 1. Clinicopathological Characteristics of 205 Patients Randomly Assigned to Either Limited Transhiatal Esophagectomy or to Extended Transthoracic Esophagectomy and Who Underwent Surgical Resection

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>THE (n = 95)</th>
<th>TTE (n = 110)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>65 (36–78)</td>
<td>62 (35–78)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>83 (87%)</td>
<td>95 (86%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>12 (13%)</td>
<td>15 (14%)</td>
<td></td>
</tr>
<tr>
<td>ASA class*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>34 (36%)</td>
<td>39 (35%)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>61 (64%)</td>
<td>71 (65%)</td>
<td></td>
</tr>
<tr>
<td>Location of tumor†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type I</td>
<td>43 (45%)</td>
<td>47 (43%)</td>
<td></td>
</tr>
<tr>
<td>Type II</td>
<td>52 (55%)</td>
<td>63 (57%)</td>
<td></td>
</tr>
<tr>
<td>Resection‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R0</td>
<td>68 (72%)</td>
<td>79 (72%)</td>
<td></td>
</tr>
<tr>
<td>R1</td>
<td>24 (25%)</td>
<td>27 (25%)</td>
<td></td>
</tr>
<tr>
<td>R2</td>
<td>3 (3%)</td>
<td>4 (3%)</td>
<td></td>
</tr>
<tr>
<td>No. positive nodes per patient§§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>3.0 (0–31)</td>
<td>4.5 (0–31)</td>
<td></td>
</tr>
<tr>
<td>No. patients with 0, 1–8, or 8+ positive nodes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>28 (29%)</td>
<td>27 (25%)</td>
<td></td>
</tr>
<tr>
<td>N1–8</td>
<td>52 (55%)</td>
<td>52 (47%)</td>
<td></td>
</tr>
<tr>
<td>N &gt; 8</td>
<td>15 (16%)</td>
<td>31 (28%)</td>
<td></td>
</tr>
</tbody>
</table>

*ASA physical status classification system.\(^7\)

†Classification according to Siewert,\(^1\) based on pathological examination of resection specimen.

‡Differences between groups were nonsignificant.

§Number of positive lymph nodes in resection specimen.

THE indicates transhiatal esophagectomy; TTE, transthoracic esophagectomy; R0, no residual tumor; R1, microscopic residual tumor; R2, macroscopic residual tumor.

### TABLE 2. Follow-up of 205 Patients Who Underwent Resection After Randomization to Either Transhiatal Esophagectomy or Transthoracic Esophagectomy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>THE (n = 95)</th>
<th>TTE (n = 110)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up (months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>26 (0–127)</td>
<td>24 (0–128)</td>
<td></td>
</tr>
<tr>
<td>Status at last follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alive</td>
<td>27 28</td>
<td>39 36</td>
<td>NS</td>
</tr>
<tr>
<td>Deceased</td>
<td>68 72</td>
<td>71 65</td>
<td>NS</td>
</tr>
<tr>
<td>In-hospital</td>
<td>1 2</td>
<td>5 7</td>
<td>NS</td>
</tr>
<tr>
<td>Without recurrence</td>
<td>8 12</td>
<td>7 10</td>
<td>NS</td>
</tr>
<tr>
<td>With recurrence</td>
<td>59 86</td>
<td>59 83</td>
<td>NS</td>
</tr>
<tr>
<td>Locoregional</td>
<td>13 19</td>
<td>16 23</td>
<td>NS</td>
</tr>
<tr>
<td>Distant</td>
<td>25 37</td>
<td>21 30</td>
<td>NS</td>
</tr>
<tr>
<td>Both</td>
<td>21 31</td>
<td>22 31</td>
<td>NS</td>
</tr>
</tbody>
</table>

THE indicates transhiatal esophagectomy; TTE, transthoracic esophagectomy; NS, nonsignificant.
whereas the pathologists decided in favor of type II relatively often. To our knowledge, this issue has never been systematically studied, but this problem is well known from clinical practice. Despite the substantial discrepancy between the endoscopic and pathologic classification, the randomization and stratification process has resulted in a well-balanced...
distribution of the 2 tumor types between the 2 treatment arms. Therefore, the impact of this potential confounder is probably limited.

In the present study, none of the patients received (neo)adjuvant chemo- and/or radiotherapy. However, many Western institutes have now incorporated neoadjuvant therapy in their standard treatment protocols. It is unclear whether the outcome of the present study would be influenced by the introduction of multimodality therapy. It is conceivable that the potential benefit of an extended lymphadenectomy is dependent on the number of positive lymph nodes. Therefore, we subdivided our patients into 3 groups: patients without positive lymph nodes in the resection specimen, patients with 1 to 8 positive nodes, and patients with more than 8 positive nodes. Theoretically, an artificially low number of positive nodes could be removed by the surgeon and identified by the pathologist after performing a limited transhiatal resection. These patients would be erroneously considered to have a limited number of positive nodes (N = 1–8), and thus contaminate this subgroup. Even though the total number of resected lymph nodes was higher after an extended lymphadenectomy, the number of positive nodes found in the resection specimen did not differ significantly between both techniques (Table 1). Therefore, the phenomenon of

![Figure 4](image_url)

**Figure 4.** A, Overall survival of patients with type I adenocarcinoma of the esophagus after transhiatal (drawn line) or transthoracic (dotted line) esophagectomy (P = 0.33). B, Overall survival of patients with type II adenocarcinoma of the gastric cardia after transhiatal (drawn line) or after transthoracic (dotted line) esophagectomy (P = 0.81).
stage migration does not seem to be of major importance in this comparison. We previously reported in 74 patients who underwent extended TTE that stage migration was mainly because of positive nodes in the upper abdomen, whereas positive subcarinal and paratracheal nodes only changed staging in a minority of patients. The present analysis shows, even though these conclusions are based on small subgroups, that an extended lymphadenectomy does not offer better locoregional disease control in patients without positive lymph nodes. Neither it is useful in patients who have many (more than 8) positive lymph nodes. It makes sense that removal of negative lymph nodes does not have an impact on disease control. Limited transhiatal resection seems to be adequate to cure patients without positive lymph nodes; a microscopically radical resection of the tumor was achieved in 72% of the patients, which is identical to the results of the extended technique (also 72%). On the other hand, patients with many (more than 8) positive lymph nodes are beyond surgical cure and probably need (additional) systemic therapy. Because the aim of a more extended resection is to gain more locoregional disease control and patients with 1 to 8 positive lymph nodes significantly benefited from

FIGURE 5. A, Locoregional disease-free survival of all patients without positive lymph nodes in the resection specimen after transhiatal (drawn line) or transthoracic (dotted line) esophagectomy ($P = 0.64$). B, Locoregional disease-free survival of all patients with 1 to 8 positive lymph nodes in the resection specimen after transhiatal (drawn line) or transthoracic (dotted line) esophagectomy ($P = 0.02$). C, Locoregional disease-free survival of all patients with more than 8 positive lymph nodes in the resection specimen after transhiatal (drawn line) or transthoracic (dotted line) esophagectomy ($P = 0.24$).
an extended lymphadenectomy with a 41% increase in 5-year locoregional disease-free survival, this subgroup of patients should be operated via the transthoracic route. It would be interesting to conduct a subgroup analysis, combining both location of the primary tumor (types I and II) and the number of positive lymph nodes in the resection specimen (N = 0, N = 1–8, N >8). Unfortunately, such combined analysis is statistically not justified because of the limited number of patients. However, only a relatively small percentage of patients with a type II tumor and a limited number of positive nodes developed a locoregional recurrence after transhiatal resection. This suggests that an extended transthoracic resection is especially beneficial in patients with a type I tumor and a limited number of positive nodes.

Then, of course, the clinical questions arises, how the number of positive nodes can be estimated before surgery. For this purpose, several diagnostic modalities are available, including endoscopic ultrasonography (EUS) combined with fine needle aspiration (FNA), CT, and PET. Until now, EUS-FNA is considered most accurate in detecting lymph node involvement with a sensitivity of 80% to 90% and a specificity of 77% to 91%. The recent combination of PET-CT seems promising by combining anatomic and metabolic information.

There are some limitations to this study. Initially, it was calculated that 220 patients had to be enrolled to detect an improvement in median survival from 14 to 22 months in patients undergoing an extended transthoracic resection with en bloc lymphadenectomy. Retrospectively, this study is underpowered, because the median survival for patients operated on via the transthiatal approach (control group) was not 14 months as initially estimated based on our historical data, but 26 months. A possible explanation for the improved survival of the transthiatal group could be the focus of the trial was on radicality of surgery and that therefore more radical transthiatal resections were achieved by more widely opening the hiatus. In the original study design, it was allowed to perform such a radical transthiatal resection in the control group and therefore this should not be considered as a methodological flaw (contamination). This is in contrast to what has been described in eg, the D1–D2 gastric cancer trial, in which the limited D1-procedure tended to become more extensive and the extended D2-procedure tended to become more limited during the course of the trial. It should be realized that in the present trial, true methodological contamination was in fact impossible, simply because a wide local resection (including the azygos vein and the thoracic duct) and a formal extended lymphadenectomy in the chest cannot be performed via the transthiatal route. Another limitation to this study is that important conclusions are drawn from a subgroup analysis (type I tumors and type II tumors). Even though it was anticipated that the location of the tumor might have an important impact on the outcome of the trial and therefore the randomization was stratified according to the tumor site, the primary end point of the study was the overall survival of both patients with type I tumors and patients with type II tumors. Ideally, our conclusions of this subgroup analysis should be tested in a new large trial. As long as this new trial has not been performed (and it seems unlikely that this trial will ever be performed), the clinical choice for the optimal surgical approach should be based on the best available evidence that comes from this largest randomized trial with complete long-term follow-up.

We, therefore, conclude after a complete follow-up of 5 years that overall survival did not differ significantly between the 2 treatment arms. However, compared with limited transthiatal resection extended TTE showed an ongoing trend towards better overall 5-year survival, especially in patients with type I esophageal adenocarcinoma. Moreover, patients with a limited number of positive nodes seemed to benefit from an extended TTE. Based on this best available evidence, we favor an extended transthoracic procedure for type I esophageal carcinoma, especially if there is a limited number of suspicious nodes, and a (limited) transthoracic procedure for type II carcinoma of the gastric cardia.

REFERENCES

**Discussions**

Professor T. Lerut: I must admit that I am biased toward this study for 2 reasons. The first is that I had the great privilege of participating in the design of the study as an external scientific advisor. The second reason is that, from a personal perspective, I very much liked one of your conclusions that, at least, for a subgroup of patients, extended lymphadenectomy seems to provide better results. But I am here to look at the paper with a more critical approach and in that respect I have a couple of comments and related questions.

First, regarding the methodology, when I compare your first publication and this manuscript, you in fact exclude 15 patients from this analysis who were included in your first publication on the intention to treat basis. On what basis were these patients now taken out and, accepting that you take them out, why did you keep the R-2 resections? Basically the result is the same whether they are irresectable or are having a R2 resection. So you should have taken out the R-2 resections as well.

Another thing that puzzles me when I compare the 2 manuscripts is that in the original manuscript there were 86 of the transhiatal and 93 of the transthoracic patients classified as type 1 tumors, whereas here, you classify 19 and 21 patients as type 1 tumors. So, these figures are different and I could not find an explanation for it in the text of your manuscript, and this goes for the type 2 tumors of the gastroesophageal junction as well, unless I missed something about the definitions.

My third remark is on the lymphadenectomy. I would think that if you would like to assess the predictive value on locoregional disease-free survival, then in my opinion, it is mandatory to avoid the confounding effect of R1 resections and R2 resections, which is about 30% and which have basically no 5-year survival. My question is, have you done the exercise of looking at the predictive value on locoregional disease-free survival, taking these R1 and R2 resections out of your calculations?

Finally, my fourth question is on how and why did you decided on the cut-off level of 8 lymph nodes? It seems to me that you decided on the basis of percentiles or, perhaps, on a stepwise analysis of the number of lymph node metastases and then relied on the P value to determine the significance. But I think, attempting to determine the critical number of lymph node metastases, other characteristics such as extra capsular lymph node involvement, the location of the tumor, the location of the nodes in terms of the distance from the primary tumor, and the type of tumors may be of equal importance, if not in themselves, independent predictors for local regional disease-free and overall survival. It looks to me like you should do a multivariate analysis on these items and I wonder whether you did this.

Miss J. Omloo: Regarding your first question, in the original paper in the New England Journal of Medicine, an intention to treat analysis was used. In this manuscript, we conducted a per protocol analysis because we thought it was better to see which operation and approach was used. We left out the patients who had perioperatively irresectable cancer because they did not actually undergo the resection. For that same reason we kept the R-1 and R-2 resection patients: because they did undergo resection.

Returning to your second question, patients were stratified according to the localization of the tumor, to a type 1 and type 2. They were stratified according to the endoscopy report. The gastroenterologists and surgeons were perhaps a bit too prone to call a tumor type 1 esophageal. For that reason several tumors were called esophageal when they were actually in the gastroduodenal region. We thought it was better to look at the actual localization site in the pathology report and that is the reason for the difference in numbers.
We did not look selectively to the R-0 resections when analyzing the impact on local-regional disease-free survival but it is a very good suggestion to do that.

As for the 8 positive lymph nodes, we decided on the cut-off according to percentiles and, because exactly 25% of the patients had no positive lymph nodes in the resection specimen, we also took the upper quartile on the other end of the spectrum and that was more than 8 positive lymph nodes.

**Professor T. Lerut:** You found a difference for the type 1 tumor. Did you also find a difference for the 2 types of tumors between the group of 1 to 8 and the others? Is there a difference between type 1 and should you also do it for the type 2 tumors?

**Miss J. Omloo:** We wanted to do that but, as our statistical advisor told us, our sample size would be too small and we would not look at a treatment effect but just at a group effect.

**Professor J. Kiss:** It is interesting that the incidence of adenocarcinoma in the United States and in Europe is rising rapidly but, in Hungary, it is not more than 10%.

Why do you not separate high-grade dysplasia, early carcinoma or the T-1 category because we treat this group of adenocarcinomas differently. If we find such a case, it is compulsory to undertake a limited distal esophageal resection with the so-called Merendino procedure. I am convinced that, in early cases, the lymph flow direction goes downwards and only in advanced cases, when the lymph vessels are blocked, the lymph flow will go upwards. So it is worthwhile to treat the early condition, the early carcinoma with only a limited resection and use the Merendino procedure? What is your opinion?

**Miss J. Omloo:** As our group published previously, patients with T-1 tumors and, especially patients with T-1 SM 2 or 3 tumors, also have a 60% risk of having positive lymph nodes anywhere away from the tumor. That is why T-1 tumors were also included in the present study.

**Professor J. Kiss:** And what about the high-grade dysplasia?

**Professor van Lanschot:** I think this is a very important question but high-grade dysplasia never metastasizes and that is why we perform an endoscopic mucosal resection. The same holds true for the T-1As. T-1A tumors hardly ever show lymphatic dissemination unlike the T-1Bs, which infiltrate into the submucosa. We undertook a separate analysis in cooperation with the Rotterdam group and we looked at about 120 patients with early tumors that were all operated via the transhiatal route. And even in those very tiny T1B tumors with positive lymph nodes, the 5-year survival rate was only 35%. So our conclusion was that, for T-1A, you can do an EMR but for T-1B there might be an advantage for an extensive resection.
Mortality After Bariatric Surgery
Analysis of 13,871 Morbidly Obese Patients From a National Registry

Mario Morino, MD,* Mauro Toppino, MD,* Pietro Forestieri, MD,† Luigi Angrisani, MD,‡ Marco Ettore Allaix, MD,* and Nicola Scopinaro, MD, FACS Hon§

Objective: To define mortality rates and risk factors of different bariatric procedures and to identify strategies to reduce the surgical risk in patients undergoing bariatric surgery.

Summary Background Data: Postoperative mortality is a rare event after bariatric surgery. Therefore, comprehensive data on mortality are lacking in the literature.

Methods: A retrospective analysis of a large prospective database was carried out. The Italian Society of Obesity Surgery runs a National Registry on bariatric surgery where all procedures performed by members of the Society should be included prospectively. This Registry represents present the largest database on bariatric surgery worldwide.

Results: Between January 1996 and January 2006, 13,871 bariatric surgical procedures were included: 6122 adjustable silicone gastric bandings (ASGB), 4215 vertical banded gastroplasties (VBG), 1106 gastric bypasses, 1988 biliopancreatic diversions (BPD), 303 biliointestinal bypasses, and 137 various procedures. Sixty day mortality was 0.25%. The type of surgical procedure significantly influenced (P < 0.001) mortality risk: 0.1% ASGB, 0.15% VBG, 0.54% gastric bypasses, 0.8% BPD. Pulmonary embolism represented the most common cause of death (38.2%) and was significantly higher in the BPD group (0.4% vs. 0.07% VBG and 0.03% ASGB). Other causes of mortality were the following: cardiac failure 17.6%, intestinal leak 17.6%, respiratory failure 11.8%, and 1 case each of acute pancreatitis, cerebral ischemia, bleeding gastric ulcer, intestinal ischemia, and internal hernia. Therefore, 29.4% of patients died as a result of a direct technical complication of the procedure. Additional significant risk factors included open surgery (P < 0.001), prolonged operative time (P < 0.05), preoperative hypertension (P < 0.01) or diabetes (P < 0.05), and case load per Center (P < 0.01).

Conclusions: Mortality after bariatric surgery is a rare event. It is influenced by different risk factors including type of surgery, open surgery, prolonged operative time, comorbidities, and volume of activity. In defining the best bariatric procedure for each patient, different mortality risks should be taken into account. Choice of the procedure, prevention, early diagnosis, and therapy for cardiovascular complications may reduce postoperative mortality.


Bariatric surgery remains the only proven mechanism for inducing both sustained and profound weight loss for morbidly obese individuals.¹–⁴ Postoperative mortality, the most feared outcome of bariatric surgery, is a rare event: published rates of postoperative mortality range from 0.05% to 2%.⁵–⁷

Detecting small (but clinically important) differences in mortality between different bariatric procedures and identifying perioperative risk factors are difficult tasks to perform in traditional cohort studies and randomized controlled trials. A recent large cohort study reported a 1.5% mortality rate after gastric bypass and identified anastomotic leak, pulmonary embolus, preoperative weight, and preoperative hypertension as associated with postoperative mortality.⁶ However, relatively few deaths were available for analysis and robust regression modeling. Furthermore, no studies have compared large series of different bariatric procedures in terms of mortality rates. The only comparative data resulted from small randomized controlled trials⁸–¹² enrolling no more than 100 patients in each group and therefore reporting only occasional deaths.

The charge of identifying differences in mortality rates and risk factors for mortality in different bariatric procedures may be ideally suited to the use of a large dataset such as a National Registry. The Italian Society of Obesity Surgery (SICOB) runs a National Registry on bariatric surgery where all procedures performed by members of the Society are included prospectively. This Registry represents, to our knowledge, the largest prospective database on bariatric surgery worldwide.

The aim of this study was to define mortality rates and risk factors of different bariatric procedures by analyzing data of the first 10 years of activity of the SICOB Registry, to identify strategies to reduce the surgical risk in patients undergoing bariatric surgery.

METHODS
The study consists of a retrospective analysis of a prospective database.
Centers were divided into 2 groups: a high case volume were correlated to each Center's global bariatric case load. Experience in bariatric procedures and in the specific physiological protocols, interval between surgery, the occurrence within 60 days of the initial procedure. The complete clinical system complications, splenic injury, hemorrhage, intestinal leak (defined complications included unexpected reoperations for surgical complications, that occurred during admissions for a bariatric surgical procedure, by codes into 2 categories: technical and systemic. Technical complications included unexpected reoperations for surgical complications, splenic injury, hemorrhage, intestinal leak (defined as any anastomotic disruptions, intestinal perforations, or staple line disruptions), occlusion, and wound complications. Systemic complications included respiratory tract, cardiac, neurologic, thromboembolic, genitourinary tract, and multi-systemic (shock) complications.

The data were evaluated to find factors related to early death. Early deaths were defined as deaths that occurred within 60 days of the initial procedure. The complete clinical report of each patient who died was examined to identify cause of death, perioperative pathological and anesthesiological protocols, interval between surgery, the occurrence of the complication and death, etc.

Each SICOB Center was identified by a progressive number and each death was correlated to the Center’s global experience in bariatric procedures and in the specific procedure that lead to patient death; furthermore, mortality rates were correlated to each Center global bariatric case load. Centers were divided into 2 groups: a high case volume hospital was defined as one that included >100 cases, a low volume hospital was defined as one that included <100 cases.

Statistical Analysis

Prospective data were collected and managed using Microsoft Excel (Microsoft Corp., Redmond, WA). This analysis was essentially a descriptive evaluation of mortality rates after bariatric procedures among different groups within the SICOB Registry cohort, and no a priori power calculation were performed.

An independent investigator examined the Registry data and the complete clinical report of each dead patient.

Preoperative patient risk factors and postoperative mortality and complications rate were compared between the different bariatric procedures and surgical approaches using \( \chi^2 \) or Fisher exact test tests for categorical variables. Two-tailed \( t \)-tests or Wilcoxon 2-sample tests were used for continuous variables depending on distribution. All \( P \) values were 2-sided. Stepwise logistic regression analysis was performed to know which predictor variables were statistically significant and correlated to the patients mortality risk. Many predictor variables were included into the analysis: sex, gender, BMI, hypertension, diabetes, hyperlipemia, surgical access, operative time, previous surgery, associated surgical procedures, and type of procedure. Some of them are dichotomous and some are continuous predictor variables. The results of analysis will be presented in a term of \( z \)-statistic from the Wald test and its \( P \) value, the standardized odds ratio, and the standard deviation of variable. A \( P \) value of 0.05 or less was considered statistically significant. Data were analyzed on an intention-to-treat basis. All calculations were done with SYSTAT (SYSTAT Software Inc., Richmond, CA).

RESULTS

Between January 1996 and January 2006, 13,871 patients submitted to bariatric surgery were enrolled in the SICOB Registry: 6122 adjustable silicone gastric bandings (ASGB), 4215 vertical banded gastroplasties (VGB), 1106 gastric bypasses (GBP), 1988 biliopancreatic diversions (BPD), 303 biliointestinal bypasses, and 137 miscellaneous procedures. Mean number of patients included per Center was 252 (range 20–1245); mean number of bariatric procedures performed each year per Center was 36 ± 33 (range 5–156). Patients submitted to biliointestinal bypasses or to miscellaneous procedures were excluded from the study because their number was insufficient for statistical analysis (no mortality occurred in this group of patients).

A total of 13,431 bariatric procedures have been included in the present study. Four thousand eight hundred fourteen (36%) procedures were performed by open surgery and 8617 (64%) by laparoscopy. Percentage of open and laparoscopic access were 3.2% (200 of 6122) and 96.8% (5922 of 6122) for ASGB; 59% (2476 of 4215) and 41% (1739 of 4215) for VBG; 38% (425 of 1106) and 62% (681 of 1106) for GBP; and 86% (1713 of 1988) and 14% (275 of 1988) for BPD, respectively.

There were 34 early deaths leading to an overall mortality of 0.25% (34 of 13,431). The type of surgical procedure followed significantly \( P < 0.001 \) mortality rates: 0.1% (6 of 6122) for ASGB, 0.15% (6 of 4215) for VBG, 0.54% (6 of 1106) for GBP, 0.8% (16 of 1988) for BPD.

Pulmonary embolism represented the commonest cause of death (13 of 34, 38.2%) and was significantly more frequent in the BPD group (0.4% BPD vs. 0.07% VBG, 0.03% ASGB, and 0% GBP) \( P < 0.01 \). Other causes of mortality were the following: cardiac failure 6 of 34 (17.6%), intestinal leak 6 of 34 (17.6%), respiratory failure 4 of 34 (11.8%), and 1 case each of acute pancreatitis, cerebral ischemia, bleeding gastric ulcer, intestinal ischemia, and internal hernia. Systemic complications represented the lead-
ing causes of death after bariatric surgery (24 of 34, 70.6%) whereas 10 of 34 (29.4%) patients died for a technical complication. Specific causes of death for each procedure are analyzed in Table 1.

Deaths occurred a mean of 20.2 ± 18.2 days from surgery (range 0–59). Systemic complications caused patients’ death after a mean of 17.4 ± 19.9 days from surgery (range 0–59). Patients with technical complications were all submitted to a reoperation a mean of 12.8 ± 13.7 days from surgery (range 4–44) and died a mean of 27 ± 14 days from the first surgical procedure (range 5–48).

The laparoscopic access reduced significantly the risk of mortality in the overall group (P < 0.001) (Table 2). In the laparoscopic group a conversion to open surgery represented a significant risk of mortality overall and among ASGB, VBG (P < 0.001), and GBP (P < 0.05) (Table 2). In particular, the laparoscopic access reduced significantly mortality because of pulmonary embolism (P < 0.01) and systemic complications (P < 0.01) (Table 3) whereas in the laparoscopic group a conversion increased significantly mortality caused by both systemic (P < 0.001) and technical (P < 0.01) complications (Table 3).

A prolonged operative time represented a significant risk factor for early deaths: mean time of surgical procedures for patients who died was 183 ± 74 minutes versus 112 ± 65 minutes (P < 0.05) (Table 4).

Sex, preoperative BMI, previous surgical, and associated surgical procedures did not significantly influence post-

### TABLE 1. Causes of Mortality After Bariatric Surgery

<table>
<thead>
<tr>
<th></th>
<th>ASGB (%)</th>
<th>VBG (%)</th>
<th>GBP (%)</th>
<th>BPD (%)</th>
<th>Overall (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary embolism</td>
<td>33.3 (2/6)</td>
<td>50 (3/6)</td>
<td>—</td>
<td>50 (8/16)</td>
<td>38.2 (13/34)</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>33.3 (2/6)</td>
<td>—</td>
<td>33.3 (2/6)</td>
<td>—</td>
<td>11.8 (4/34)</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>33.3 (2/6)</td>
<td>16.6 (1/6)</td>
<td>16.6 (1/6)</td>
<td>12.5 (2/16)</td>
<td>17.6 (6/34)</td>
</tr>
<tr>
<td>Cerebral ischemia</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>6.2 (1/16)</td>
<td>2.9 (1/34)</td>
</tr>
<tr>
<td>Intestinal leak</td>
<td>—</td>
<td>33.3 (2/6)</td>
<td>33.3 (2/6)</td>
<td>12.5 (2/16)</td>
<td>17.6 (6/34)</td>
</tr>
<tr>
<td>Bleeding gastric ulcer</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>6.2 (1/16)</td>
<td>2.9 (1/34)</td>
</tr>
<tr>
<td>Acute pancreatitis</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>6.2 (1/16)</td>
<td>2.9 (1/34)</td>
</tr>
<tr>
<td>Internal hernia</td>
<td>—</td>
<td>—</td>
<td>16.6 (1/6)</td>
<td>—</td>
<td>2.9 (1/34)</td>
</tr>
<tr>
<td>Intestinal ischemia</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>2.9 (1/34)</td>
<td>2.9 (1/34)</td>
</tr>
<tr>
<td>Systemic complications (total)</td>
<td>100 (6/6)</td>
<td>66.6 (4/6)</td>
<td>50 (3/6)</td>
<td>68.8 (11/16)</td>
<td>70.6 (24/34)</td>
</tr>
<tr>
<td>Technical complications (total)</td>
<td>0 (0/6)</td>
<td>33.3 (2/6)</td>
<td>50 (3/6)</td>
<td>31.2 (5/16)</td>
<td>29.4 (10/34)</td>
</tr>
</tbody>
</table>

ASGB indicates adjustable silicone gastric banding; VBG, vertical banded gastroplasty; GBP, gastric bypass; BPD, biliopancreatic diversion.

### TABLE 2. Correlation Between Mortality Risk and Surgical Approach

<table>
<thead>
<tr>
<th></th>
<th>Open Surgery Death (%)</th>
<th>Laparoscopy Death (%)</th>
<th>Converted Laparoscopy Death (%)</th>
<th>P</th>
<th>Converted Laparoscopy Death (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASGB</td>
<td>0.5 (1/200)</td>
<td>0.08 (5/5922)</td>
<td>0.06</td>
<td>0.07 (4/5844)</td>
<td>1.3 (1/78)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VBG</td>
<td>0.12 (3/2476)</td>
<td>0.17 (3/1739)</td>
<td>—</td>
<td>0.06 (1/1680)</td>
<td>3.4 (2/59)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GBP</td>
<td>0.47 (2/425)</td>
<td>0.58 (4/681)</td>
<td>—</td>
<td>0.45 (3/661)</td>
<td>5 (1/20)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>BPD</td>
<td>0.93 (16/1713)</td>
<td>0 (0/275)</td>
<td>&lt;0.05</td>
<td>0 (0/254)</td>
<td>0 (0/21)</td>
<td>NS</td>
</tr>
<tr>
<td>Overall</td>
<td>0.46 (22/4814)</td>
<td>0.14 (12/8617)</td>
<td>&lt;0.001</td>
<td>0.09 (8/8439)</td>
<td>2.25 (4/178)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

ASGB indicates adjustable silicone gastric banding; VBG, vertical banded gastroplasty; GBP, gastric bypass; BPD, biliopancreatic diversion; NS, not significant.

### TABLE 3. Rate of Different Lethal Complications After Open, Laparoscopic, or Converted Bariatric Procedures

<table>
<thead>
<tr>
<th></th>
<th>Open Surgery Death (%)</th>
<th>Laparoscopy Death (%)</th>
<th>P</th>
<th>Successful Laparoscopy Death (%)</th>
<th>Converted Laparoscopy Death (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary embolism</td>
<td>0.21 (10/4814)</td>
<td>0.03 (3/8617)</td>
<td>&lt;0.01</td>
<td>0.02 (2/8439)</td>
<td>0.56 (1/178)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other systemic complications</td>
<td>0.12 (6/4814)</td>
<td>0.06 (5/8617)</td>
<td>NS</td>
<td>0.05 (4/8439)</td>
<td>0.56 (1/178)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Total systemic complications</td>
<td>0.33 (16/4814)</td>
<td>0.09 (8/8617)</td>
<td>&lt;0.01</td>
<td>0.07 (6/8439)</td>
<td>1.1 (2/178)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Technical complications</td>
<td>0.12 (6/4814)</td>
<td>0.05 (4/8617)</td>
<td>NS</td>
<td>0.04 (3/8439)</td>
<td>0.56 (1/178)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Total</td>
<td>0.45 (22/4814)</td>
<td>0.14 (12/8617)</td>
<td>&lt;0.001</td>
<td>0.1 (9/8439)</td>
<td>1.7 (3/178)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

ASGB indicates adjustable silicone gastric banding; VBG, vertical banded gastroplasty; GBP, gastric bypass; BPD, biliopancreatic diversion; NS, not significant.
operative mortality neither overall nor among single procedures (Table 4). Concerning age there was a significant difference only among patients submitted to ASGB ($P < 0.05$) (Table 4).

Concerning preoperative comorbidities, hypertension ($P < 0.01$) and diabetes mellitus ($P < 0.05$) but not hyperlipemia did significantly influence the risk of mortality (Table 5).

The risk of mortality did significantly correlate with bariatric case load per center: mortality rate in high volume hospitals was 0.19% versus 0.51% in low volume hospitals ($P < 0.01$) (Table 6). Stepwise logistic regression has selected only the pulmonary embolism as statistically significant. The multivariate analysis confirmed this variable as an independent predictor of mortality patients risk (odds ratio 149.2; $z$ 10.6; $P < 0.001$).

**DISCUSSION**

The analysis of the SICOB Registry identifies an overall mortality risk for bariatric surgery of 0.25% and 5 different factors influencing mortality risk: type of procedure, surgical access (laparoscopic or open), operative time, preoperative comorbidities, and hospital bariatric case volume.

The type of surgical procedure was significantly correlated with the risk of mortality: mortality rates were 0.1% for ASGB, 0.15% for VBG, 0.5% for GBP, and 0.8% for BPD. It is interesting to note that mortality of GBP, the most commonly performed procedure worldwide, in the present study corresponds to the 0.5% 30 days mortality rate reported by Buchwald in a review and meta-analysis of GBP. 7 Complex surgical procedures including intestinal sutures and anastomosis have an increased risk of mortality both from technical and systemic complications. Until now, no studies have compared large series of different bariatric procedures in terms of mortality rates. Recent publications from large administrative dataset have reported contrasting data on early deaths after bariatric surgery. Using the Nationwide Inpatient Sample database, Santry et al19 reported a 0.2% in-hospital mortality; this mortality rate contrasts with the 1.9% mortality at 30 days for Washington State reported by Flum et al5 The remarkably low mortality rate from the Nationwide Inpatient Sample study presumably underestimates total postoperative mortality, as this database detects only deaths that occurred during the hospitalization in which the procedure was performed. Nevertheless, these 2 US studies were cen-

| TABLE 4. Influence of Different Parameters on Mortality |
|---------------------------------|---|---|
| Mortality Rate                  | 100 Cases | >100 Cases |
| No. Cases Enrolled              | ASGB | VBG | GBP | BPD | Overall |
| ASGB                            | 0.19 (2/1056) | 0.08 (4/5066) | NS |
| VBG                             | 0.58 (2/345) | 0.1 (4/3870) | <0.05 |
| GBP                             | 0.89 (2/225) | 0.45 (4/881) | NS |
| BPD                             | 0.83 (6/724) | 0.79 (10/1264) | NS |
| Overall                         | 0.51 (12/2350) | 0.19 (22/11081) | <0.01 |

ASGB indicates adjustable silicone gastric banding; VBG, vertical banded gastroplasty; GBP, gastric bypass; BPD, biliopancreatic diversion; NS, not significant.
tered on GBP, a procedure that represents 88% of bariatric procedures in the United States but only 8.2% in the present series. In Europe restrictive procedures (particularly ASGB) were extremely popular in the last decade and, in the SICOB Registry, represented 74% of all procedures performed in the study period. The recent introduction and diffusion of laparoscopic ASGB in the United States is at present slowly modifying surgical attitude of US bariatric surgeons and the significant difference in mortality risks between laparoscopic ASGB and laparoscopic GBP (0.1% vs. 0.5%) is a point to be taken into account.

Systemic complications, pulmonary and cardiovascular above all, represent 70% of mortality causes, ranging from 100% for ASGB to 50% for GBP (Table 1). Although all patients included in the Registry underwent perioperative prophylaxis of thromboembolic complications, including low molecular weight heparin and graduate elastic compression stockings, pulmonary embolism represented the commonest single cause of death (38%). Technical complications causing death were essentially related to the presence of intestinal sutures or anastomosis varying from 0% in ASGB to 33% and 37% in VBG and BPD and to 50% in GBP. Among technical complications, intestinal leaks were the most common; accordingly, leaks have been reported as the first cause of death in many GBP series.

Different randomized controlled trials have shown that the laparoscopic approach was advantageous for ASGB, VBG, and GBP but because of the limited number of patients they all failed to show a reduced mortality rate in laparoscopic patients. The present study shows that the laparoscopic access significantly reduces the mortality risk in bariatric surgery, mainly by reducing systemic complications such as cardiac and respiratory failure and pulmonary embolism.

On the other side, among patients submitted to laparoscopic bariatric surgery conversion represents a significant risk of early deaths (2.25% vs. 0.09%; P < 0.001), increasing the rate of all types of systemic and technical complications (Table 3). This figure corresponds to data reported in other applications of laparoscopic surgery such as colorectal and hepatobiliary.

The role of comorbidities in increasing mortality risk after GBP has been shown by Jamal et al and Weller et al among others. Our data clearly show that preoperative hypertension and diabetes are significant risk factors for mortality after all bariatric procedures.

It is well known in abdominal surgery that systemic complications and particularly pulmonary embolism are more frequent after prolonged surgical procedure. The present study identifies prolonged operative time as a further risk factor for bariatric surgery. Therefore, a complex laparotomic operation involving digestive suture and anastomosis with a prolonged operative time presented a high risk for pulmonary embolism, the first cause of death in the present series.

The volume-outcome relationship has been well established in several complex abdominal operations; however, few studies have examined this relationship in patients undergoing bariatric surgery. In a recent study Nguyen et al demonstrated that bariatric surgery performed at hospitals with more than 100 cases annually is associated with a lower morbidity and mortality (0.3% vs. 1.2%, P < 0.01); this volume-outcome relationship was even more pronounced for a subset of patients older than 55 years, for whom in-hospital mortality was 3-fold higher at low-volume compared with high-volume hospitals. The study by Nguyen et al referred uniquely to GBP; the present series, including 74% of restrictive procedures (ASGB and VBG), confirms that case volume load significantly affects mortality rates after bariatric surgery. Specifically, hospitals that performed 1 to 100 procedures during the study period had a mortality rate of 0.51% whereas those who performed >100 procedures had a mortality rate of 0.19% (P < 0.01).

In conclusion, this national study confirms that mortality after bariatric surgery is a rare event. Nevertheless, different risk factors, such as, type of procedures, open surgery, prolonged operative time, presence of comorbidities, and low volume hospitals could be identified.

Bariatric surgery is a potentially life-saving procedure in selected patients and in the hands of a qualified surgeon. A correct evaluation of the identified risk factors for early mortality may help to optimize outcomes in these elective procedures.

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REFERENCES


Discussions

PROFESSOR R. MARGREITER: Dr Morino and his colleagues should be congratulated, not only for having established what I think is the largest database in bariatric surgery, but also for this careful analysis. The overall mortality is very low. It has to be mentioned, however, that the majority of their procedures were of a restrictive nature. Seventy percent of their deaths were due to systemic complications and about 40% of them were due to pulmonary embolism. According to your manuscript, all patients were given low molecular weight heparin prophylactically. My question is what dosage was used and for how long was it given in these patients, since it has been reported that this complication may occur even late after surgery and that anticoagulation should therefore be given for at least 4 weeks?

Heart failure accounted for about 17% of deaths. Since laparoscopy may impair cardiac function, I would ask whether those 6 cardiac deaths occurred in the open or in the laparoscopic group and did these deaths occur early or later (ie, more than one week or so after surgery?)

There were a few leaks, 6 altogether. How were these leaks managed, by stenting or did you redo the anastomosis? And could you maybe tell us what the leakage rate was in this last series?

You say that volume had an impact on mortality. The handling of these morbidly obese patients is certainly always the same. The various procedures, however, differ in their surgical complexity and it could well be that a single center performed 500 gastric bandings without mortality but the only gastric bypass patient died.
Finally, have you done any multivariate analyses and what was the outcome?

PROFESSOR M. MORINO: Concerning DVT prophylaxis: I cannot give the protocol of every center but most used a standard protocol: 0.4 unit to 0.8 unit of low molecular heparin will be given from the day before surgery up to 20–28 days after surgery. Furthermore, most of groups used compressive stockings. Laparoscopy allowed early mobilization, a goal that is not easy to reach after open surgery in obese patients. I think that the data on pulmonary embolism are very interesting because, while in the majority of procedures laparoscopy did not reduce the rate of pulmonary embolism, in the present series of bariatric surgery pulmonary emboli were significantly reduced after laparoscopy compared with laparotomy. Concerning the heart problem, unfortunately I cannot give you data for each patient but certainly, in every center, the patients are evaluated preoperatively and severe heart problems are a contraindication to laparoscopy in every center. Nevertheless, you must balance the advantages of laparoscopy for an obese patient, with the disadvantages of the risk of left sided cardiac problems. This evaluation is done on a single basis per patient together with the anesthesiologist.

Concerning leaks and their management, in the present series we reported only 6 leaks because 6 leaks led to death. But, as you know, the leaks are in the range of 2% and therefore this should be approximately the overall leakage rate in the SICOB Registry. The main problem is that, in obese patients, a leak has a large variety of clinical impacts. It can be difficult to diagnose a leak in an obese patient. Sometimes they do not have any clinical problem, they seem perfect but they have a leak. In the present series this problem is probably enhanced by the fact that these patients were operated upon a mean of 12 days following surgery. One patient for instance was operated on 44 days after surgery, so, certainly, this patient was treated conservatively in the first instance with a percutaneous drainage and then, because of the persistence of the leak, had to be operated on. It changes very much from one case to another but, certainly, you have to be very, very careful in following these patients. Another point is that with laparoscopy, everybody obtains very early gastro-esophageal x-rays, and sometimes they may be done too early. In the first day you may not see a leak that appears 2 or 3 days later, when the patient is already eating.

As for the volume caseload: your question is correct. The volume caseload is significant for each procedure, even in the bandings, which represent a simple procedure, there are more deaths in the group who with fewer banding.

Concerning the multivariate analysis, the only significant independent risk factor for mortality was pulmonary embolism.

PROFESSOR A. SITGES-SERRA: I have a couple of questions. Do you provide some checking for the honesty and completeness of data? Do you visit the participant centers? How sure are you that everybody reports the deaths? In your country as well as mine, in south Europe, there is much pressure in the media on that and people tend to hide these complications.

Also, are these so-called learning curves included in that study? At what level of expertise do these centers start to include patients because that could also be a bias?

If we eliminate gastric banding, almost all the figures double and then you have increasing mortality figures because gastric banding accounts for almost half of the patients you recruited in the study.

And finally, your paper is a good example of statistical versus clinical significance. The massive series is so huge that even 0.2% or 0.1% differences are significant. However, the relevance of clinical significance versus statistical significance could be a matter of debate.

PROFESSOR M. MORINO: I will start from the last point. In my opinion, the clinical significance of a 0.1% or 0.2% difference in mortality after bariatric surgery is extremely important. Each death in this case means a legal process and means being on the media and on the news. This is a special group of patients.

Certainly checking would be ideal. We discussed this, but we have not gone into checking for the moment. SICOB is more or less a group of friends. We know each other very well. I hope that their data are correct. I must say that, once again, a patient who dies after bariatric procedure, at least in Italy, goes into the newspapers so it is very easy to check because they are in the press and television.

Concerning the learning curve, the main problem is that the Registry represents the results of an expert group of surgeons that covers presumably less than half of bariatric surgery in our country. It would be very interesting to compare our results with the standard results all over the country. Very often in congresses I have heard that gastric banding is abandoned but, in fact, more and more people are doing banding and lap band represents by and large the most common bariatric procedure worldwide. Furthermore, gastric banding is coming to the United States now because they received FDA approval only a few years ago. Even in the United States, the number of bandings is increasing. I think that the mortality data are important in this set. I think that banding will stay with us for a long time in the future.

PROFESSOR N. SENNINGER: I have 3 questions. One relates to Body Mass Index, which you did not mention at all. Is there a relation to Body Mass Index?

The second is, and I think everyone would agree, the 2 major procedures that will evolve are gastric bypass and gastric banding. We know that we see more problems in the early postoperative course after gastric bypass, but we see more problems after gastric banding in the long term. Were you able
to study the morbidity of the patients with gastric banding in the long term? During the last year we removed more than 6 gastric bands endoscopically with some problems.

And, finally, what worried me most is that you could show that the time for the reoperation was about 12 days for those patients who died. This is a time when most of our patients, or at least this is the aim, are already discharged from hospital. How many of these patients had to be readmitted, and should this encourage us to keep an eye on these patients for a longer period of time?

Professor M. Morino: BMI is not statistically significant but there is a slight difference. The mean BMI of the whole group was 44 and 48 for the group who died, but it is not statistically significant.

We could stay here for 2 days talking of bypass and bands! We know the problem of banding very well. We described the first series of banding removals in '95 in the British Journal of Surgery. The surgeon and the patient must choose between something very safe and simple that gives inferior results in terms of weight loss and more complication in the long term and a complex procedure with a non-negligible mortality that gives better results in the long term. This is a matter of choice between surgeon and patient.

And finally, regarding time of reoperation, there is a recent series from the United States where many patients were dismissed one or 2 days after surgery, had problems at home, came back and died after rehospitalization. This is not the case in Italy. Our laparoscopic bypass patients stay more or less 4 days in hospital. So, usually, any complications arise during this period. The reason for a mean of 12 days before reoperation is not that the patient was at home and then came back to the hospital, but just because the treatment was, in the first instance, conservative.
Objective: The primary goal of this study was to clarify whether a laparoscopic (LPS) approach could be considered the dominant strategy in patients undergoing right colectomy.

Summary Background Data: Because few nonrandomized or small sized studies have been carried out so far, definitive conclusions about the role of LPS right colectomy cannot be drawn.

Methods: Two hundred twenty-six patients, candidates for right colectomy, were randomly assigned to LPS (n = 113) or open (n = 113) resection. The postoperative care protocol was the same for both groups. Trained members of the surgical staff who were not involved in the study registered postoperative morbidity. Follow-up was carried out for 30 days after hospital discharge. The following costs were calculated: surgical instruments, operative room occupation, routine care, postoperative morbidity, and hospitalization.

Results: Conversion rate in the LPS group was 2.6% (3 of 113). Operative time (in minutes) was longer in the LPS group (131 vs. 112, P = 0.01). Postoperative morbidity rate was 18.6% in the open group and 13.3% in the LPS group (P = 0.31). Postoperative stay was one day longer in the open group (P = 0.002). No difference was found in postoperative quality of life. The additional operative charge in the LPS group was €980 per patient randomized (€821 for surgical instruments and €159 for longer operative time). The savings in the LPS group was €390 per patient randomized (€144 for shorter length of hospital stay and €246 for the lower cost of postoperative morbidity). The net balance resulted in a €590 extra charge per patient randomly allocated to the LPS group.

Conclusion: LPS slightly improved postoperative recovery. This translated into a savings that covered only 40% of the extra operative charge. Therefore, open right colectomy could be still considered an effective procedure.


Available data from the literature show that laparoscopic (LPS) colorectal resection is associated with earlier postoperative recovery and shorter length of hospital stay (LOS) compared with open technique.1–3 does not adversely affect oncologic outcome,4–6 and has a favorable cost-benefit balance.7,8

However, randomized clinical trials carried out on LPS colorectal surgery so far included different types of operations (right colectomy, left colectomy, sigmoid resection, and rectal resection), and consequently their results and relative conclusions cannot be automatically translated to each of these procedures. In particular, LPS and open right colectomy are quite similar with respect to surgical technique. In fact, only bowel mobilization and vascular pedicle division are usually performed intracorporeally during LPS right colectomy, whereas bowel division and ileocolonic anastomosis are usually performed extracorporeally.9 Therefore, the potential benefits of LPS right colectomy over open technique could be less relevant compared with other colorectal procedures.

Because few nonrandomized or small sized clinical trials focusing only on right colectomy have been reported,10–14 further studies are necessary to clearly demonstrate the superiority of a LPS approach.

The primary end point of the present study is to evaluate postoperative outcome in a single institutional series including 226 patients undergoing right colectomy, who were randomly allocated to either LPS or open surgery. A cost-benefit analysis and quality of life assessment were also carried out.

METHODS

Adult patients undergoing right colectomy admitted to our department were assessed for study eligibility throughout a 5-year period. Inclusion criteria were age ≥18 years and suitability to elective surgery. Exclusion criteria were cancer infiltrating adjacent organs assessed by computed tomography, cardiovascular dysfunction (New York Heart Association class >3), respiratory dysfunction (arterial pO2 < 70 mm Hg), hepatic dysfunction (Child-Pugh class C), ongoing infection, and plasma neutrophil level < 2.0 × 10^9/L.

The study was approved by the Ethical Committee of the San Raffaele Hospital. The study design was explained to the potential participants who were asked to sign a written informed consent before randomization.
Eligible participating patients were randomly allocated to LPS or open surgery. A randomization list was generated by a computer program. Assignments were made by means of sealed sequenced masked envelopes that were opened, before the induction of anesthesia, by a nurse unaware of the trial design. A subgroup of patients was included in a previous study. They also decided the day of surgery (adhesions due to previous surgery in 2 groups was found with respect to operative blood loss, rate of transfused patients, and reoperation rate (Table 2). Three (2.6%) patients in the LPS group needed conversion to open surgery (adhesions due to previous surgery n = 2, bleeding n = 1). These patients remained in the LPS arm for data analysis. Reoperation was necessary in 3 (2.6%) patients in the LPS group (2 intestinal obstructions, 1 anastomotic leak) and in 5 (4.4%) patients in the open group (3 anastomotic leaks, 1 intestinal obstruction, 1 bleeding). All patients of both groups had midline incision. Mean (SD) incision length was 5.3 (0.6) cm in the LPS group and 14.1 (2.1) cm in the open group (P = 0.0001).

RESULTS

Figure 1 shows the diagram of the trial according to the CONSORT statement. Of the 226 patients randomized, 113 were assigned to the LPS group and 113 to the open group.

The 2 groups were well balanced for demographics and preoperative parameters (Table 1). In cancer patients the number of lymph nodes harvested was 17.2 (SD 7.3) in the LPS group and 16.3 (SD 6.9) in the open group. In all neoplastic patients resection margins were cancer free.

The duration of surgery was 19 minutes shorter in the open group (P = 0.01). No significant difference between the 2 groups was found with respect to operative blood loss, rate of transfused patients, and reoperation rate (Table 2). Three (2.6%) patients in the LPS group needed conversion to open surgery (adhesions due to previous surgery n = 2, bleeding n = 1). These patients remained in the LPS arm for data analysis. Reoperation was necessary in 3 (2.6%) patients in the LPS group (2 intestinal obstructions, 1 anastomotic leak) and in 5 (4.4%) patients in the open group (3 anastomotic leaks, 1 intestinal obstruction, 1 bleeding). All patients of both groups had midline incision. Mean (SD) incision length was 5.3 (0.6) cm in the LPS group and 14.1 (2.1) cm in the open group (P = 0.0001).

Cost-benefit analysis was based on the following costs: surgical instruments, operative room (OR) (£502 per hour), routine surgical care, diagnosis, and treatment of postoperative complications. To calculate the cost of each postoperative complication the following items were assessed: laboratory and microbiology analysis; medical, technical, and diagnostic services; surgical and therapeutic interventions; medications; prolonged LOS; and ambulatory follow-up consultations. The mean LOS of uncomplicated patients was the basis to calculate the prolonged LOS in each patient with complication. In patients who developed multiple complications, resources used to treat each complication were recorded separately.

Statistical Analysis

Sample size was calculated assuming 25% overall 30-day morbidity rate in the open group in accordance with our previous series and a reduction to 10% in the LPS group. Admitting a type I error level of 0.05 and a power of 0.80, at least 113 patients in each group were required. All patients were analyzed on an intention-to-treat basis. Descriptive data are reported as mean (standard deviation), median and range, or number of patients and percentage. Comparison between groups for discrete variables was made by the χ² test. Student test was used to compare normally distributed variables. The P value <0.05 was considered to indicate statistical significance (2-tailed test).
TABLE 1. Demographics and Clinical Characteristics of Patients

<table>
<thead>
<tr>
<th>Variable*</th>
<th>Laparoscopy (n = 113)</th>
<th>Open (n = 113)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>64.8 (13.7)</td>
<td>66.7 (13.2)</td>
<td></td>
</tr>
<tr>
<td>Men/Women</td>
<td>58/55</td>
<td>51/62</td>
<td></td>
</tr>
<tr>
<td>ASA score</td>
<td>1.96 (0.64)</td>
<td>2.02 (0.51)</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (g/L)</td>
<td>11.5 (2.1)</td>
<td>11.6 (2.4)</td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>9 (7.9%)</td>
<td>7 (6.2%)</td>
<td></td>
</tr>
<tr>
<td>Undernutrition</td>
<td>13 (11.5%)</td>
<td>12 (10.6%)</td>
<td></td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>35.8 (5.8)</td>
<td>35.3 (5.5)</td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>97 (85.8%)</td>
<td>94 (83.2%)</td>
<td></td>
</tr>
</tbody>
</table>

Data are number of patients (%) or mean (standard deviation). *No significant difference between groups (minimum P = 0.26).
ASA indicates American Society of Anesthesiologist.

TABLE 2. Surgical Details

<table>
<thead>
<tr>
<th>Operative Variable</th>
<th>Laparoscopy (n = 113)</th>
<th>Open (n = 113)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of surgery (min)</td>
<td>131 (37)</td>
<td>112 (69)</td>
<td>0.01</td>
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<tr>
<td>Operative blood loss (mL)</td>
<td>132 (168)</td>
<td>168 (194)</td>
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<td>Transfused patients</td>
<td>12 (10.6%)</td>
<td>17 (15.0%)</td>
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<tr>
<td>Reoperation</td>
<td>3 (2.6%)</td>
<td>5 (4.4%)</td>
<td>0.67</td>
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<tr>
<td>Conversion</td>
<td>3 (2.6%)</td>
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<td>—</td>
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</table>

Data are number of patients (%) or mean (standard deviation).

TABLE 3. Patients With 30-day Morbidity

<table>
<thead>
<tr>
<th>Complication</th>
<th>Laparoscopy (n = 113)</th>
<th>Open (n = 113)</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>Overall</td>
<td>15 (13.3)</td>
<td>21 (18.6)</td>
<td>0.31</td>
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<tr>
<td>Infectious*</td>
<td>8 (7.1)</td>
<td>10 (8.8)</td>
<td>0.77</td>
</tr>
<tr>
<td>Noninfectious*</td>
<td>6 (5.3)</td>
<td>9 (8.0)</td>
<td>0.55</td>
</tr>
<tr>
<td>Anastomotic leak*</td>
<td>2 (1.8)</td>
<td>4 (3.5)</td>
<td>0.62</td>
</tr>
<tr>
<td>Mortality</td>
<td>1 (0.9)</td>
<td>0 (0.0)</td>
<td>0.90</td>
</tr>
</tbody>
</table>

All values within parenthesis indicate percentage values. *Numbers of single type of complication do not add up to the number of overall complications within the 2 groups, in relation to the possible occurrence of more type of complications in some patients.

No significant difference was found in the number of patients who developed postoperative complications at the 30-day follow-up (Table 3). One patient of the LPS group died in the postoperative course (massive upper gastrointestinal bleeding). Table 4 shows postoperative complications in detail. In both groups about 40% of postoperative infections occurred after discharge.

The mean (SD) postoperative stay was 5.4 (1.8) days (median 5, range 4 –21) in the LPS group and 6.4 (2.8) days (median 5, range 5–39) in the open group (P = 0.002). Recovery of oral food intake occurred after 2.1 (0.9) days in the LPS and 3.0 (1.2) days in the open group (P = 0.0001).

Long-term morbidity occurred in 1 (0.9%) patient of the LPS group who needed reoperation for incisional hernia and in 4 (3.5%) patients of the open group (3 incisional hernia, 1 small bowel obstruction) (P = 0.4). In the open group readmission was necessary in 3 of 4 patients (2 reoperations for incisional hernia, 1 conservative treatment for small bowel obstruction).

At 2-year follow-up, systemic recurrence occurred in 10 (10.3%) cancer patients of the LPS group and in 8 (8.5%) cancer patients of the open group. Local recurrence occurred in 1 patient of both groups.

Figure 2 shows postoperative quality of life. No significant difference between the 2 groups was found 6 and 12 months after surgery.

Cost-Benefit Analysis

The mean extra charge of LPS surgical instruments was €821 per patient randomized. The longer OR occupancy resulted in €159 additional charge per patient randomized to LPS. Therefore, the additional OR charge in the LPS group was €980 per patient randomized (Table 5).

One hundred ninety (84.1%) patients had an uneventful postoperative course (LPS n = 98, open n = 92). In these patients the mean cost of routine care was the same in both groups (€288/d), whereas the mean postoperative stay was 5.1 days in the LPS group and 5.6 days in the open group. This translated in €144 saving per patient randomized in the LPS group.

The cost of postoperative complications was €49,455 in the LPS group and €77,259 in the open group. This resulted in €27,804 saved in the LPS group (€246 per patient randomized). The overall savings per patient randomized in the LPS
group due to both shorter LOS and lower cost of complications was €390. Considering the additional OR charge in the LPS group (€980), there was €590 extra charge per patient randomly allocated to the LPS group.

**DISCUSSION**

Because several authors reported that LPS colonic resection for cancer did not increase local or systemic recurrence rate,4,6,16 a detailed analysis of clinical and economic parameters could orient the decision process in considering LPS approach as the gold standard for colonic resections, regardless of the site of disease.1,7,8,18 However, no reliable data are still available about LPS right colectomy because studies carried out so far are nonrandomized or small sized.9–14

LPS right colectomy is more similar to the open technique in comparison with other colonic resections, mainly because bowel division and anastomosis are usually performed extracorporeally. This technique allows a low conversion rate and a reasonable operative duration.9 Moreover, findings about lymph node sampling and resection margins support the concept that LPS allowed an adequate cancer clearance. Experiences with intracorporeal anastomosis are scanty because it is technically difficult, longer, and it requires a long training period.19

Our results show that LPS is associated with an earlier postoperative recovery and a shorter LOS in accordance with previous reports.10,11,18,20,21 However, the standard application of an early-recovery-after-surgery protocol also in open group minimized the advantages of LPS in our series. In fact, we found a minimal shorter LOS (1 day) after LPS right colectomy in comparison with more relevant reductions of LOS after LPS rectal resection or mixed series of colorectal resections.2,7,16

No significant difference was found in short-term morbidity rate according to previous reports in a prospective nonrandomized comparative series10 or in case control series.11–13 Moreover, general health, and physical and social functioning were comparable between LPS and open groups. Conversely, in series of colorectal cancer patients we found that LPS was associated with a significant improvement of quality of life in the first 12 months after surgery.16,22 All these findings support the concept that the clinical benefits of LPS seem less pronounced after right colectomy in comparison with rectal resection or series of mixed colorectal procedures.1,2,7,16,22

A major drawback of LPS is its high cost. In view of the worldwide increasing concerns over escalating costs in medical care, the decision process for adopting new routine treatments should be informed by cost-benefit analyses of clinical trials. All studies dealt with cost-benefit analysis showed that the cost of LPS colorectal resection was substantially higher in comparison with open technique because of both longer operation and more expensive surgical instruments.7,8,23 However, the better postoperative short-term outcome in the LPS group balanced the operative extra charges.7,8

Previous cost-benefit analyses on LPS right colectomy were performed in small sized nonrandomized series with contrasting results.10,12,20,24 Two studies reported that LPS was more expensive, mainly for the high operative charges,10,24 one found no difference between LPS and open technique,12 whereas other 2 studies carried out in patients with Crohn’s disease reported that the reduction of postoperative costs in the LPS group more than offset the higher operative charges.20,21 However, in all these studies the open group was not given an early-recovery-after-surgery protocol and the impact on hospital costs of health care resources consumed to treat postoperative morbidity was not precisely assessed.

The present cost-benefit analysis showed that in the LPS group the savings caused by both shorter LOS and lower postoperative morbidity rate covered only 40% of the OR extra charge. Besides €590 extra cost per patient randomized, LPS right colectomy allowed an earlier postoperative recovery and a cosmetic advantage because of shorter incision length. However, this did not translate to either a lower postoperative morbidity or an improved quality of life.

In conclusion, LPS right colectomy resulted in an earlier postoperative recovery however morbidity rate and quality of life after surgery were similar to open procedure. Because the cost-benefit analysis showed a relevant additional charge in the LPS group, open right colectomy still remains an effective procedure.

**REFERENCES**


Discussions

Professor R. O’Connell: I have a number of questions. The first is how many years did it take to complete this study because of the very large number of patients and how many staff surgeons were involved? Was this restricted to a few very experienced surgeons or was this something that was open to residents and a greater number of surgeons?

The second issue is that you dealt comprehensively with the visible costs but I do not think you have dealt with the hidden costs of providing a laparoscopic program. By this, I mean the prolonged period of training that is needed to reach the level of expertise needed to perform right hemicolectomy with such good results, a low conversion rate and low morbidity. Also, I wonder if you have any sense of the costs entailed in the investment for a dedicated laparoscopic operating room. These costs are often assessed and are not factored into an analysis such as you have presented.

Finally, I wonder if you might have missed the potential benefit in quality of life by waiting to assess it until 6 and 12 months postoperatively. One would expect that any benefit in terms of quality of life after right hemicolectomy would manifest maybe 1 and 3 months postoperatively and not so long after surgery.

Professor M. Braga: First of all, our study period was 5 years. All operations, both laparoscopic and open surgery, were performed by 3 trained senior surgeons.

The second point you raised focuses on other costs. I think that we must split these costs into 2 groups. The first one is represented by the social cost after discharge. It is very difficult to calculate it in a precise way because, for instance, the social cost for retired patients is different from the social cost for working patients. The second group includes the cost of training and the cost of a dedicated laparoscopic operation room. So far, no study has included these costs. Including these costs in the analysis probably would reinforce our conclusion.

The third question focuses on quality of life. In a previous study we calculated the time to recover to preoperative performance in colorectal cancer patients. It was about 32 days after laparoscopic surgery and 65 days after open surgery. In general, a potential bias in the early evaluation of quality of life in cancer patients could be adjuvant chemotherapy. This was the reason why we preferred to assess quality of life 6 months or 1 year after surgery. When we prolonged the observation, there was no difference between groups at 2 years and more.

Professor M. Morino: I have 2 points. The majority of costs in the laparoscopic group, €820 (approximately $1150 US), relates to the use of disposable instruments. You can have a very different attitude towards instruments. Two years ago we showed, in a randomized study published in Annals of Surgery, (December 2005;242:6), that ultracision is not necessary, especially for right hemicolectomy. Furthermore, a single disposable trocar could be sufficient for colorectal surgery. At least, this is our attitude. I think you can scale these costs down considerably.

Your conclusions in terms of costs are similar in the 2 groups. Do you think that the volume of the tumor has an importance, especially on the right side? Sometimes the tumor is a very big and bulky one and you have to make a big incision. Could tumor volume be an important variable and could the final message be—go for laparoscopy for a smaller tumor and for open for a bigger tumor?

Professor M. Braga: I agree with you about your first question. We decided to standardize our approach by using the same instruments for the whole period of the study. One potential development of this study is to reduce the cost of
laparoscopic instruments. So, the use of a harmonic scalpel is probably not necessary in all patients.

The second questions asks in which cases can we advise the use of laparoscopic procedures, ie, how can we select patients? I agree with you about the size of the tumor. I think that open procedure is better in patients with a large tumor. In a previous experience we found that preoperative risk factors associated with immune dysfunction, like homologous blood transfusion or severe weight loss, disappeared with a laparoscopic approach. Therefore, transfused patients, severely undernourished patients, and elderly patients could benefit more from a laparoscopic approach. Looking at the future, we should select which patients can be candidates for either laparoscopy or an open approach.

Professor N. Senninger: It should also be emphasized that short stay or fast-track concepts with open surgery are bringing profit to the patient. We should not forget that there is evidence that, in patients where you have to convert from a laparoscopic procedure because of the tumor, open surgery may be required because you are getting into false contact with the tumor. These patients are faring considerably less well than the ones where you can avoid this oncologic problem from the beginning. At the moment, there is no clear algorithm as to how to select the patients, so we are really looking forward to the point that you are making. You mentioned that the cost of additional training must be taken into account. Hardly any of the studies do this, and we would be glad if, in the future, you could show us how much these costs would contribute to the overall cost evaluation.

Professor A. Sitges-Serra: I have 2 questions and 1 comment. The first is do you perform the open procedure from midline or through a transversal flank?

Professor M. Braga: Midline in both groups.

Professor A. Sitges-Serra: With a flank transverse incision we are talking about a 5 cm difference, which may also help the open procedure.

My second comment is in regard to what the additional costs would be if the anastomosis was made by mechanical suture. You are cost-conscious because you are undertaking a hand sewn anastomosis but many surgeons use a mechanical technique. How much more would that cost?

Professor M. Braga: The extra cost of mechanical anastomosis is about €250 (approximately $350 US) in our hospital. When we were not using a laparoscopic approach but undertook open surgery, mechanical anastomosis allowed about 15 minutes to spare. Therefore, mechanical anastomosis is probably not cost effective.

Professor A. Sitges-Serra: I have 1 final comment. I have been preaching eco-surgery for some time. When I see kilograms of plastic being thrown out after sophisticated laparoscopic procedures, I say, “My goodness, where is all this plastic going?” We should be more environmentally conscious and include recycling costs in the future.

Professor J. Mendes de Almeida: I would like you to comment on 2 issues. First, I think that you spend a lot of money doing the operation laparoscopically. In my hospital, just using the ultracision, the harmonic scalpel costs €400 (approximately $560 US) and you do not need it to do the operation. Secondly, you can reduce costs if you use reusable trocars, as we do. So I think that, in your study, the emphasis on operative costs of laparoscopic surgery is very for what you can actually achieve.

Laparoscopic surgery, mainly the more difficult and complicated procedures, requires a fast-track protocol, and you are not using a very aggressive fast-track surgery protocol. You are using epidural and analgesia for 3 days. Our goal for dismissal of the patient for right hemicolecctiony is on the third operative day and you are still using epidural and analgesia at that time. My questions is what would the results of your study be if you reduced costs by using reusable material, not using a harmonic scalpel, and using a more aggressive fast-track protocol that laparoscopically operated patients tolerate very well with the new analgesics that are available?

Professor R. O’Connell: It sounds to me that that is the next study!

Professor M. Braga: In our experience, we did not find such a significant difference in tolerating fast-track between laparoscopic and open surgery. The most important advantages derived from fast-track were experienced in the open group. I agree with you that it is possible to be more aggressive with fast-track but, in our country, it is not so easy to discharge patients very early because we have about one-third of patients from the south of Italy. Moreover, our home care service is not optimal so there are many reasons why we prefer to keep patients in the ward for 4 or 5 days.
Randomized Trial of Argon Plasma Coagulation Versus Endoscopic Surveillance for Barrett Esophagus After Antireflux Surgery: Late Results

Tim Bright, MBBS, FRACS,* David I. Watson, MD, FRACS,* William Tam, PhD, FRACP,† Philip A. Game, MBBS, FRCS, FRACS,‡ David Astill, PhD, FRCPA,§ Roger Ackroyd, MD, FRCS, FRCSEd,¶ Bas P. L. Wijnhoven, MD, PhD,* Peter G. Devitt, MS, FRCS, FRACS,‡ and Mark N. Schoeman, PhD, FRACP†

Objective: To determine the efficacy of endoscopic argon plasma coagulation (APC) for ablation of Barrett esophagus.

Summary Background Data: APC has been used to ablate Barrett esophagus. However, the long-term outcome of this treatment is unknown. This study reports 5-year results from a randomized trial of APC versus surveillance for Barrett esophagus in patients who had undergone a fundoplication for the treatment of gastroesophageal reflux.

Methods: Fifty-eight patients with Barrett esophagus were randomized to undergo either ablation using APC or ongoing surveillance. At a mean 68 months after treatment, 40 patients underwent endoscopy follow-up. The efficacy of treatment, durability of the neosquamous re-epithelialization, and safety of the procedure were determined.

Results: Initially, at least 95% ablation of the metaplastic mucosa was achieved in all treated patients. At the 5-year follow-up, 14 of 20 APC patients continued to have at least 95% of their previous Barrett esophagus replaced by neosquamous mucosa, and 8 of these had complete microscopic regression of the Barrett esophagus. Five of the 20 surveillance patients had more than 95% regression of their Barrett esophagus, and 4 of these had complete microscopic regression (1 after subsequent APC treatment). The length of Barrett esophagus shortened significantly in both study groups, although the extent of regression was greater after APC treatment (mean 5.9 – 0.8 cm vs. 4.6 – 2.2 cm). Two patients who had undergone APC treatment developed a late esophageal stricture, which required endoscopic dilation, and 2 patients in the surveillance group developed high-grade dysplasia during follow-up.

Conclusions: Regression of Barrett esophagus after fundoplication is more likely, and greater in extent, in patients who undergo ablation with APC. In most patients treated with APC the neosquamous mucosa remains stable at up to 5-year follow-up. The development of high-grade dysplasia only occurred in patients who were not treated with APC.


The incidence of esophageal adenocarcinoma continues to increase rapidly in Western countries.1 Barrett esophagus is the main risk factor for the development of this cancer. Although most esophageal adenocarcinomas present in patients who are not known to have Barrett esophagus,2 many patients with Barrett esophagus are currently enrolled in endoscopic surveillance programs. This is because surveillance-detected esophageal adenocarcinomas are usually identified at an earlier stage, and consequently these patients have a better survival outcome.3,4 It has been argued that the risk of progression of Barrett esophagus to cancer is greatest in patients in whom reflux is poorly controlled. This highlights the importance of effective antireflux therapy in these patients. Unfortunately, most patients with Barrett esophagus will not have complete regression of the columnar-lined mucosa with either effective medical or surgical therapy. These patient will remain at a higher risk of developing esophageal cancer.5-8 For this reason, there has been interest in reversing Barrett esophagus using mucosal ablation techniques. The aim of these therapies is to destroy the metaplastic columnar mucosa, after which a neosquamous epithelium will usually form in the region of the destroyed mucosa. Control of reflux during the period of mucosal regeneration is important for the formation of the neosquamous epithelium because the intraluminal environment in the esophagus seems to influence the pattern of mucosal healing.
Studies with short-term follow-up have shown that endoscopic treatment with argon plasma coagulation (APC) can achieve a reduction, or complete reversal, in the length of Barrett esophagus.2,3 Most patients develop a complete neosquamous esophageal epithelium after APC treatment, although some patients have some residual Barrett esophagus or buried Barrett esophagus mucosa beneath the neosquamous mucosa. We have previously confirmed these findings with the early (12 months) outcomes from a randomized trial of APC ablation versus surveillance for Barrett esophagus in patients who had previously undergone a successful antireflux operation.4 However, the durability of the neosquamous mucosa after APC ablation, and the ability of ablative therapies to reduce cancer risk has not been determined. In this study we determined the longer term outcomes of our randomized trial of APC ablation versus surveillance for Barrett esophagus.

METHODS

The patients and methods for this trial have been described in detail in an earlier report.4 In brief, patients aged between 18 and 75 years with known Barrett esophagus, who had previously undergone a fundoplication for gastroesophageal reflux disease were invited to participate. Barrett esophagus was confirmed at enrollment by the endoscopic appearances of ectopic columnar mucosa, with histopathological evidence of specialized columnar epithelium (with intestinal metaplasia). Patients with high-grade dysplasia (HGD), endoscopic evidence of ulcerative oesophagitis, or reflux symptoms were excluded.

Patients were then randomized to undergo either annual endoscopic surveillance or APC ablation of their Barrett esophagus. At the initial endoscopy, the length and percentage of the circumference of the esophagus covered by ectopic columnar mucosa was determined. Four quadrant biopsies were taken using large cup disposable biopsy forceps, commencing 1 cm above the gastroesophageal junction and every 2 cm above for the length of the Barrett esophagus (as per modified “Seattle” protocol). Patients randomized to surveillance underwent annual endoscopy, and biopsies were taken as per the original protocol.

In patients randomized to undergo ablation treatment, the columnar epithelium was cauterized by APC as described previously.5 Complete ablation was attempted at the first endoscopy in patients with short segments of Barrett esophagus (less than 3 cm). To reduce the risk of stricture formation, and to minimize postprocedure pain, the treatment of long segments of Barrett esophagus was limited to 50% of the circumference of the esophagus, up to a maximum length of 5 cm in a single treatment session. Treatment was repeated every 4 weeks until either complete (or at least 95%) squamous re-epithelialization had occurred or a maximum of 6 treatments had been undertaken. Four weeks after the last APC treatment, a further endoscopy was performed, and biopsies were taken at the site of the previous biopsies.

Further endoscopies were scheduled every 12 months in both groups of patients. The endoscopic findings were recorded, and 4 quadrant biopsies were taken from the same sites in the neosquamous or the columnar mucosa on each occasion. The biopsies were examined by a pathologist who was unaware of whether ablation had been undertaken.

Before commencing this study, it was determined that to show a 30% difference in the rate of complete ablation of Barrett esophagus between the study groups at a significance level (2-sided) of $P < 0.05$ and a power of 90%, 16 patients would be required in each of the study groups. Differences between the 2 study groups were determined using a 2-tailed unpaired $t$ test or Mann–Whitney $U$ test when comparing continuous variables, and Fisher exact test when analyzing $2 \times 2$ contingency tables. Changes in the length of Barrett esophagus at different time points were analyzed using a paired $t$ test. Statistical significance was set at a $P$ value of $<0.05$.

The protocol for this study was approved by the Human Clinical Research Ethics Committee of the Royal Adelaide Hospital, and the Flinders Clinical Research Ethics Committee.

RESULTS

Fifty-eight patients were entered into this trial between August 1999 and November 2005. At enrollment, reflux symptoms were fully controlled in all patients, and none of the patients were using acid suppressant medication. Initial endoscopy assessment showed no evidence of active gastroesophageal reflux, and appearances were consistent with an intact fundoplication in all patients.

Of the 58 trial patients, 40 patients (20 in each group) were enrolled into the study more than 5 years ago and have undergone endoscopy assessment more than 4 years after initial enrollment. The outcome for these patients was determined for this report. All of these patients had undergone a previous 360-degree angle Nissen fundoplication. The 2 study groups were well matched (Table 1). The mean duration of follow-up was 68 months (range 50–74)

<table>
<thead>
<tr>
<th>TABLE 1. Demographic Data</th>
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<td></td>
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<td>Cigarettes (Y:N)</td>
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<td>Time postfundoplication at intake (months)</td>
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</table>
in the APC group, and 71 months (range 60–72) in the surveillance group.

The median number of treatment sessions in the group undergoing ablation with APC was 2.5 (range 1–6). All 20 patients allocated to APC ablation had at least 95% reduction in surface area of their Barrett esophagus at the initial post-APC endoscopy (1 month posttreatment) and 14 had no macroscopic evidence of Barrett esophagus. At 12 months follow-up 1 patient had recurrence of Barrett esophagus. The fundoplication in this patient had failed, and this was subsequently revised by open surgery. At late follow-up, 14 of the 20 APC patients continued to have at least 95% reduction of the surface area of the Barrett esophagus, and 8 of these had no macroscopic or histologic evidence of Barrett esophagus. In the surveillance group, 3 of 20 patients had a 95% or greater reduction in the surface area of Barrett esophagus at 12 months. This increased to 5 patients at late follow-up, with 3 of these patients having no macroscopic or histologic evidence of Barrett esophagus at the most recent endoscopy. One of these patients, however, had developed HGD at earlier follow-up, and then underwent APC ablation treatment. This was followed by macroscopic (but not complete histologic) regression of the Barrett esophagus and dysplasia. The number of patients in the APC group with 95% or more reduction in Barrett esophagus at late follow-up was significantly greater (70% vs. 20%, \( P = 0.0036 \), Fisher exact test) than that in the surveillance group (having excluded the surveillance patient who underwent APC for HGD).

At entry into the study, the length of Barrett esophagus in both groups was similar (\( P = 0.31 \) (Table 2). In both groups the average length of Barrett esophagus at late follow-up was significantly less (\( P < 0.0001 \) – APC group; \( P < 0.0001 \) – surveillance group). At late follow-up, the reduction in the length of Barrett esophagus in the APC group was significantly greater than that in the surveillance group (\( P = 0.0277 \)).

Of the patients who had no macroscopic evidence of Barrett esophagus at endoscopy, 3 of 11 patients in the APC group, and 2 of 5 in the surveillance group had some columnar cells present in biopsies taken from presumed neosquamous epithelium. Apart from the surveillance patient who underwent APC, these glands were not buried glands. However, buried glands were noted in 2 APC patients at their pretreatment endoscopy, one of whom continued to have buried glands at 5 years. Another 2 APC patients had buried glands at their last endoscopy. Two surveillance patients also had buried glands during follow-up. The surveillance patient who had APC for HGD had buried glands both pre- and post-APC. The extent of the Barrett esophagus and regression is summarized in Table 3.

There were no early complications in this study. At later follow-up 2 patients developed strictures after APC treatment. One of these patients had had 6 APC treatments for a 12-cm length of Barrett esophagus. He developed a stricture 18 months after treatment, and this resolved after 4 endoscopic dilations. The other patient underwent 4 APC treatment sessions for a 6-cm length of Barrett esophagus. He developed a stricture 5 years after APC treatment, and this was managed by a single endoscopic dilation.

One patient in the APC group had low grade dysplasia (LGD) at the initial endoscopy. A second patient developed LGD during follow-up. Neither of these patients had LGD at their most recent endoscopy. None of the surveillance group had LGD at the initial endoscopy. Two developed LGD during follow-up. In 1 of these patients dysplasia was not seen at the most recent endoscopy, whereas in the other LGD was diagnosed at the 5-year endoscopy. During follow-up, none of the patients who had undergone APC treatment progressed to HGD or adenocarcinoma, whereas in the surveillance group 2 patients developed HGD. One of the patients who developed HGD was not fit for esophagectomy and hence underwent APC treatment (see above). The other continued in surveillance when a second endoscopy did not confirm HGD and has remained stable with LGD at subsequent endoscopies.

**DISCUSSION**

Barrett esophagus is recognized to be the major risk factor for the development of adenocarcinoma of the esophagus, a malignancy which continues to become more common in Western countries. Patients who are known to have Barrett esophagus are usually followed by regular endoscopic examination, often within the context of a formal surveillance program. Currently, there is much interest in therapies, which might reverse the metaplastic process of Barrett esophagus, and possibly the risk of esophageal cancer.

A range of strategies for ablation of Barrett esophagus have been described. These include photodynamic therapy, mucosal resection, radiofrequency ablation, and APC.

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**TABLE 2.** Mean Length of Barrett Mucosa at Intake and at 5 Years as Assessed by Endoscopy

<table>
<thead>
<tr>
<th>APC Group</th>
<th>Surveillance Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length (cm) of Barrett Esophagus</td>
<td>Length (cm) of Barrett Esophagus</td>
</tr>
<tr>
<td>Initial endoscopy (before treatment)</td>
<td>5.9 (range 2–13)</td>
</tr>
<tr>
<td>Endoscopy at 5 yr</td>
<td>0.8 (range 0–3)</td>
</tr>
</tbody>
</table>

**TABLE 3.** Extent of Barrett Esophagus and Regression at 5-Year Follow-Up

<table>
<thead>
<tr>
<th>Extent of Regression</th>
<th>APC Group</th>
<th>Surveillance Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endoscopic and histologically complete regression</td>
<td>8</td>
<td>4*</td>
</tr>
<tr>
<td>Endoscopically complete regression, but some columnar mucosa present histologically</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Endoscopic regression 95%–99%</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Endoscopic regression &lt;95%</td>
<td>6</td>
<td>15</td>
</tr>
</tbody>
</table>

*One of these patients developed high-grade dysplasia and then underwent APC treatment.
These techniques all aim to remove or destroy the metaplastic columnar mucosa. If the associated reflux problem is controlled by appropriate medical or surgical therapy, then the regenerating mucosa will usually be squamous in type. However, it is not known whether this regenerated mucosa is less likely to progress to cancer. In the setting of HGD, a study has shown that ablation has been shown to significantly decrease (13% c.f. 28%) the risk of progressing to adenocarcinoma when compared with surveillance alone.

There are differing opinions about which ablative therapy is best. APC has the advantage of using widely available equipment, which can be found in most endoscopy units. However, it is operator dependent because the APC applicator must be aimed accurately at the appropriate area of mucosa. Nevertheless, the technique of APC ablation can be easily taught and in our experience the learning curve is short.

There are few reports of ablative therapies in patients who have undergone a surgical fundoplication for the control of reflux. Most studies have investigated patients whose reflux was treated with proton pump inhibitor medication. In the published postsurgical APC ablation studies, the length of follow-up has been relatively short, with the mean duration of follow-up being 17\textsuperscript{18} and 31.9 months.\textsuperscript{19} Successful initial neosquamous re-epithelialization was achieved in more than 90% of patients in these studies, and similar outcomes have been reported for ablation using bipolar electrocoagulation\textsuperscript{20} and endoscopic laser\textsuperscript{21} in patients who had undergone a previous fundoplication.

The longer term results of APC ablation in patients whose reflux is controlled by medication are more variable. Mork et al\textsuperscript{23} reported that 72% of patients using proton-pump inhibitors who had APC ablation of their Barrett esophagus had at least some recurrence of Barrett esophagus at a mean 30 months follow-up. At a median 36 months follow-up, Kahaleh et al\textsuperscript{15} reported a 62% recurrence rate in patients who were taking 20 to 40 mg omeprazole daily. In contrast, Madisch et al\textsuperscript{12} reported a relapse rate of only 3% per annum at median follow-up of 51 months. The patients in the latter study were taking very high dose proton-pump inhibitor therapy (120 mg omeprazole daily), suggesting that the completeness of acid suppression might influence the success of ablative therapy.

Our study has confirmed that at 5 to 6 years follow-up the neosquamous epithelium formed after APC ablation of Barrett esophagus in postfundoplication patients is relatively stable. At late follow-up, 40% of the APC group had no macroscopic or histologic evidence of Barrett’s. This compares to our previously reported rate of 50% at baseline and 55% of patients at 12 months after ablation.\textsuperscript{11} All APC patients had >95% reduction in their Barrett’s initially after APC, 80% had >95% at 1 year, and 70% maintained this reduction in Barrett esophagus at 5 years.

Interestingly, at late follow-up, significant regression of Barrett esophagus occurred in the postfundoplication patients who had not undergone ablation, although the extent of regression was less than that seen after APC treatment. Furthermore, both the baseline and the late endoscopies were performed after the fundoplication had been performed. This is an important observation, because the anatomy in these patients was stable, and the regression seen in the surveillance group cannot be attributed to any anatomic rearrangements, which occur with the construction of a fundoplication. Three of the patients in the surveillance group had complete spontaneous macroscopic regression of their Barrett esophagus during follow-up. All of these patients had a 2-cm length of Barrett esophagus at baseline. It has been noted previously that fundoplication alone is associated with regression of Barrett esophagus in 20% of patients,\textsuperscript{8,24} and our results are consistent with these observations. The rate of spontaneous regression after surgery is greater than the 2% rate of regression in patients treated with medication reported in a study of 123 patients.\textsuperscript{6}

The only patients who developed HGD in our study were in the surveillance group. In addition to the 2 patients reported, a third patient in the surveillance group who has only undergone 3 years follow-up in this trial developed HGD and successfully underwent an esophagectomy. However, the number of patients who have reached the end point of HGD are insufficient for a statistically significant difference to be demonstrated. To address this, we are continuing to follow-up the patients enrolled in this study, and we are recruiting more patients so that the size of the study groups can be expanded. Nevertheless, our results show fundoplication alone does not prevent the development of HGD in Barrett esophagus.\textsuperscript{25,26}

Recent reports have raised concerns about the risk of malignancy developing after ablation. Unexpected cases of cardia nodules and dysplasia\textsuperscript{27} or adenocarcinoma of the cardia after APC have been reported.\textsuperscript{28} In cases of incompletely eradicated Barrett esophagus, islands of columnar epithelium have been shown to have Ki-67 and p-53 biomarker abnormalities, which are not seen in neosquamous epithelium in completely eradicated Barrett esophagus.\textsuperscript{29} However, this concern about incompletely ablated Barrett esophagus has not been reflected in the clinical outcomes of the APC group in our study.

The implications of postablation squamous re-epithelialization resulting in “buried” Barrett tissue are uncertain. There have been cases of adenocarcinoma arising from columnar tissue covered by squamous tissue.\textsuperscript{30} The magnitude of this risk is unknown. Hornick et al\textsuperscript{11} have reported reduced expression of some biomarkers in columnar mucosal tissue found beneath squamous epithelium, compared with columnar mucosa found in adjacent areas. This suggests that the overlying squamous epithelium could actually provide protection from the injurious effects of reflux, and reduce the risk of cancer. That complete protection of columnar tissue from the refluxate seems to be beneficial, adds support to the hypothesis that surgical control of reflux with a fundoplication, might reduce the risk of cancer.

Although there were no initial complications (perforation or hemorrhage) from APC therapy, with follow-up beyond 12 months 2 patients developed an esophageal stricture requiring dilation. Both had multiple APC treatments for long segments of Barrett esophagus. Strictures have been reported previously after APC,\textsuperscript{10,32} although more commonly after...
photodynamic therapy treatment. The development of a stricture probably relates both to the depth of ablation and whether it is performed circumferentially. It was perhaps surprising, however, that stricture formation occurred at late follow-up. This confirms that ablation with APC is not a benign procedure, although in both instances the stricture was easily dealt with by endoscopic dilatation.

A limitation of our study is the lack of formal 24 hour pH monitoring at 5 years. However, all patients had excellent control of reflux symptoms, and there was no clinical evidence of variance in reflux control between the APC and surveillance groups. Furthermore, there was no clinical evidence that the patients who developed HGD had recurrent reflux. Although intuitively, restoration of a normal esophageal pH seems necessary for squamous re-epithelialization after Barrett ablation, it can occur in the setting of abnormal pH studies. However, sustained long-term re-epithelialization has been found to be associated with pH normalization.

In conclusion, the late results from this randomized trial confirm sustained regression of Barrett esophagus in both treated and untreated patients, although the extent of regression is greater in patients who undergo ablative therapy with APC. Although the only patients who developed HGD during follow-up were in the surveillance arm, longer term follow-up and larger patient numbers are required to demonstrate any reduction in cancer risk. Although the ablation of nondysplastic Barrett esophagus seems to be promising, further studies are required before it can be considered for routine clinical practice.

REFERENCES

Laparoscopic Surgery Is Associated With a Lower Incidence of Venous Thromboembolism Compared With Open Surgery

Ninh T. Nguyen, MD, Marcelo W. Hinojosa, MD, Christine Fayad, BS, Esteban Varela, MD, MPH, Viken Konyalian, MD, Michael J. Stamos, MD, and Samuel E. Wilson, MD

Background: Although laparoscopy now plays a major role in most general surgical procedures, little is known about the relative risk of venous thromboembolism (VTE) after laparoscopic compared with open procedures.

Objective: To compare the incidence of VTE after laparoscopic and open surgery over a 5-year period.

Patients and Interventions: Clinical data of patients who underwent open or laparoscopic appendectomy, cholecystectomy, antireflux surgery, and gastric bypass between 2002 and 2006 were obtained from the University HealthSystem Consortium Clinical Database. The principal outcome measure was the incidence of venous thrombosis or pulmonary embolism occurring during the initial hospitalization after laparoscopic and open surgery.

Results: During the 60-month period, a total of 138,595 patients underwent 1 of the 4 selected procedures. Overall, the incidence of VTE was significantly higher in open cases (271 of 46,105, 0.59%) compared with laparoscopic cases (259 of 92,490, 0.28%, P < 0.01). Our finding persists even when the groups were stratified according to level of severity of illness. The odds ratio (OR) for VTE in open procedures compared with laparoscopic procedures was 1.8 [95% confidence interval (CI) 1.3–2.5]. On subset analysis of individual procedures, patients with minor/moderate severity of illness level who underwent open cholecystectomy, antireflux surgery, and gastric bypass had a greater risk for developing perioperative VTE than patients who underwent laparoscopic cholecystectomy (OR: 2.0; 95% CI: 1.2–3.3; P < 0.01), antireflux surgery (OR: 24.7; 95% CI: 2.6–580.9; P < 0.01), and gastric bypass (OR: 3.4; 95% CI: 1.8–6.5; P < 0.01).

Conclusions: Within the context of this large administrative clinical data set, the frequency of perioperative VTE is lower after laparoscopic compared with open surgery. The findings of this study can provide a basis to help surgeons estimate the risk of VTE and implement appropriate prophylaxis for patients undergoing laparoscopic surgical procedures.


Venous thromboembolism (VTE) is a major cause of morbidity and mortality in patients undergoing gastrointestinal surgery. It is estimated that 600,000 patients developed pulmonary embolism (PE) each year in the United States. The incidence of fatal PE ranges from 0.1% to 0.8% in patients undergoing elective general surgical procedures. Since the early 1990s, laparoscopy has revolutionized the field of gastrointestinal surgery. The acceptance rate for laparoscopic surgery has been overwhelming for general surgical procedures such as cholecystectomy, appendectomy, and even Roux-en-Y gastric bypass for the treatment of morbid obesity. Although well accepted as the procedure of choice for many general surgical procedures, the incidence of VTE after laparoscopic gastrointestinal procedures is not well defined.

Certain factors associated with laparoscopic surgery, such as early ambulation and a reduction in postoperative hypercoagulability, may reduce the risk of VTE. However, intraoperative factors associated with laparoscopic surgery have been shown to possibly increase the risk of VTE. The use of intraoperative pneumoperitoneum and reverse Trendelenburg position are independent factors for reduction of femoral venous flow and, combined with prolonged operative times associated with laparoscopic procedures, may increase the risk for VTE. Although the true incidence of VTE after laparoscopic compared with open surgery is unknown, most investigators recommend that thromboprophylaxis in laparoscopic surgery should be the same as those for conventional open surgery. Understanding the relative risk for development of VTE after laparoscopic compared with open surgery will help surgeons with the selection of appropriate thromboprophylaxis for their laparoscopic procedures. There have been no large studies examining the incidence of VTE after laparoscopic compared with open surgery. The objective of this study was to determine the incidence of clinically evident...
VTE during the initial hospitalization after laparoscopic compared with open surgery for 4 commonly performed gastrointestinal surgical procedures—appendectomy, cholecystectomy, antireflux surgery, and Roux-en-Y gastric bypass.

**MATERIALS AND METHODS**

**Discharge Data Set**

The University HealthSystem Consortium (UHC) database is an administrative, clinical, and financial database that provides benchmark measures on the utilization of health care resources for the purpose of comparative data analysis between academic institutions. The UHC database is a collection of patient-level, discharge-abstracted data from academic health centers and affiliate community hospitals. It contains discharge information on inpatient hospital stay including patient characteristics, length of stay, overall and specific postoperative morbidity, and observed and expected (risk-adjusted) in-hospital mortality. One of the benefits of the UHC Clinical Database is the risk-adjusted data for comparison of institutions. To accomplish risk adjustment, the UHC uses regression-modeling techniques in combination with 3M Health Information Systems, Agency for Healthcare Research and Quality comorbidity software, and the UHC complication profiler to assign a severity of illness level, and assign an expected length of stay, costs, and probability of mortality to every patient in the database. The assignment of severity of illness level is based on a combination of principal and secondary diagnoses to define different levels of severity and complexity of treatment. The 4 severity of illness categories are minor, moderate, major, and extreme severity. For example, comorbidities such as diabetes would be categorized as moderate severity and recent myocardial infarction as extreme severity. Complication is defined as the percentage of patients who developed the particular complication before being discharged from the hospital. The UHC database has no information available on complications occurring after discharge, even if the complication occurred within 30 days from the date of surgery. Length of stay was defined as the period from the index procedure to hospital discharge. Approval for the use of the UHC patient-level data in this study was obtained from the Institutional Review Board of the University of California, Irvine Medical Center and the UHC.

**Study Cohort**

We analyzed the UHC hospital discharge records of all patients who were 18 years or older and who underwent 1 of 4 commonly performed gastrointestinal procedures—appendectomy, cholecystectomy, antireflux surgery, and Roux-en-Y gastric bypass. Hospital discharge records for appendectomy and cholecystectomy were reviewed between January 1, 2002 and December 31, 2006 and records for antireflux surgery and gastric bypass cases were reviewed between October 1, 2004 and December 31, 2006. The specific ICD-9 procedure code for laparoscopic gastric bypass only first became available on October 1, 2004. All procedures were performed on an inpatient basis. Unfortunately, there is no information available on the use or nonuse of thromboprophylaxis or about the type (mechanical or antithrombotics) and duration of prophylaxis. Analysis of the 4 gastrointestinal procedures required the use of appropriate diagnosis and procedural codes as specified by the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). These 4 procedures were selected because they have both the laparoscopic and open ICD-9 procedural codes for their respective procedures. The ICD-9-CM diagnosis and procedure codes for the 4 procedures are listed in Table 1. For appendectomy, the principal ICD-9 diagnosis codes for acute appendicitis and perforated appendicitis were used. Perforated appendicitis included a subcategory for generalized peritonitis or peritoneal abscess. For cholecystectomy, the principal ICD-9 diagnosis codes for cholelithiasis, acute cholecystitis, and chronic cholecystitis were used. We analyzed elective and urgent/emergent procedures for appendectomy and cholecystectomy groups. For antireflux surgery, the principal ICD-9 diagnosis codes for esophagitis, esophageal reflux, and Barrett esophagus were used. For gastric bypass, the principal ICD-9 diagnosis codes for obesity and morbid obesity were used, which included a subcategory of obesity and a subclassification of morbid

### TABLE 1. ICD-9-CM Diagnosis and Procedure Codes Used to Define Laparoscopic and Open Procedures

<table>
<thead>
<tr>
<th>Principal Diagnosis</th>
<th>ICD-9-CM</th>
<th>Principal Procedure</th>
<th>ICD-9-CM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute appendicitis</td>
<td>540.0, 540.9, 541, 542</td>
<td>Laparoscopic appendectomy</td>
<td>47.01</td>
</tr>
<tr>
<td>Perforated appendicitis</td>
<td>540.0, 540.1</td>
<td>Open appendectomy</td>
<td>47.0, 47.09</td>
</tr>
<tr>
<td>Cholelithiasis</td>
<td>574.2, 574.20, 574.2</td>
<td>Laparoscopic cholecystectomy</td>
<td>51.23</td>
</tr>
<tr>
<td>Acute cholecystitis</td>
<td>574.0, 574.00, 574.01, 575.0, 571.2</td>
<td>Open cholecystectomy</td>
<td>51.22, 51.21</td>
</tr>
<tr>
<td>Chronic cholecystitis</td>
<td>574.10, 575.11, 574.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esophageal reflux</td>
<td>530.81</td>
<td>Laparoscopic antireflux surgery</td>
<td>44.67</td>
</tr>
<tr>
<td>Esophagitis</td>
<td>530.10, 530.11, 530.12, 530.19</td>
<td>Open antireflux surgery</td>
<td>44.65, 44.66</td>
</tr>
<tr>
<td>Barrett esophagus</td>
<td>530.85</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morbid obesity</td>
<td>278.0, 278.01, 278.00</td>
<td>Laparoscopic gastric bypass</td>
<td>44.38</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Open gastric bypass</td>
<td>44.31, 44.39</td>
</tr>
</tbody>
</table>
obesity. The principal ICD-9 procedure codes for open Roux-en-Y gastric bypass included a subcategory of gastroenterostomy without gastrectomy and a subclassification of high gastric bypass and the principal ICD-9 procedure code for laparoscopic Roux-en-Y gastric bypass included a subcategory of gastroenterostomy without gastrectomy and a subclassification laparoscopic gastroenterostomy. To increase the homogeneity of the cohort, the diagnosis related group (DRG) for operative treatment of obesity (DRG 288) was also used to examine the data for gastric bypass. For antireflux surgery and gastric bypass surgery, we only analyzed elective procedures; patients undergoing urgent and emergent procedures were excluded.

Definition of Outcomes

The overall rate of venous thrombosis and PE after laparoscopic and open surgery for the 4 surgical procedures and the individual rate of VTE after appendectomy, cholecystectomy, antireflux surgery, and gastric bypass were examined. The diagnosis of venous thrombosis and PE during the hospitalization for laparoscopic and open surgery was based on the presence of a secondary diagnosis of an ICD-9 CM code for venous thrombosis and/or PE. Patients with primary diagnosis of phlebitis, thrombophlebitis, PE, or venous thrombosis (classified according to DRG) were excluded.

Statistical Analysis

We compared patient characteristics (age, sex, race, and severity class), length of hospital stay, overall rate of VTE after laparoscopic versus open surgery, and the individual rate of VTE after laparoscopic versus open appendectomy, cholecystectomy, antireflux surgery, and gastric bypass. The rate of VTE after laparoscopic versus open surgery was also examined according to the level of severity of illness. Data are expressed as mean ± SD. Differences in patient characteristics and VTE between laparoscopic versus open group were analyzed using Fisher exact test or the Pearson’s χ² test. Univariate analysis was performed and the 95% confidence interval (CI) of the odds ratio (OR) was obtained. Continuous variables were compared using Student t tests. Statistical analysis was performed using Epi Info statistical software, version 3.3.2 (CDC, Atlanta, GA). A P value of less than 0.05 was considered significant.

RESULTS

From 2002 to 2006 a total of 138,595 patients, 84,650 of whom were female (61%), underwent 1 of the 4 selected

TABLE 2. Summary of Demographics of Patients Undergoing Open Versus Laparoscopic Appendectomy, Cholecystectomy, Antireflux Surgery, and Gastric Bypass Operations, 2002 to 2006

<table>
<thead>
<tr>
<th></th>
<th>Open Procedure*</th>
<th>Laparoscopic Procedure*</th>
<th>P²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No. cases</td>
<td>46,105</td>
<td>92,490</td>
<td>—</td>
</tr>
<tr>
<td>Female gender, No. (%)</td>
<td>22,342 (48.5)</td>
<td>62,308 (67.4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Age, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–30 yr</td>
<td>12,180 (26.3)</td>
<td>22,868 (24.7)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>31–50 yr</td>
<td>17,799 (38.4)</td>
<td>38,963 (42.0)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>51–64 yr</td>
<td>9530 (20.5)</td>
<td>18,799 (20.3)</td>
<td>0.2</td>
</tr>
<tr>
<td>≥65 yr</td>
<td>6857 (14.8)</td>
<td>12,089 (13.0)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Race, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>26,951 (58.1)</td>
<td>55,292 (59.6)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>African American</td>
<td>6211 (13.4)</td>
<td>12,001 (12.9)</td>
<td>0.02</td>
</tr>
<tr>
<td>Severity of illness, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor</td>
<td>22,729 (49.0)</td>
<td>54,660 (59.0)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Moderate</td>
<td>18,415 (39.7)</td>
<td>32,065 (34.6)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Major</td>
<td>3876 (8.4)</td>
<td>5058 (5.5)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Extreme</td>
<td>1347 (2.9)</td>
<td>935 (1.0)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Admission status, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elective</td>
<td>11,265 (24.3)</td>
<td>32,451 (35.0)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Urgent</td>
<td>7452 (16.1)</td>
<td>12,640 (13.6)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Emergency</td>
<td>27,650 (59.6)</td>
<td>47,628 (51.4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Length of hospital stay (days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appendectomy</td>
<td>3.4 ± 3.0</td>
<td>2.2 ± 2.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Cholecystectomy</td>
<td>7.2 ± 6.9</td>
<td>3.3 ± 4.3</td>
<td>0.04</td>
</tr>
<tr>
<td>Antireflux surgery</td>
<td>3.9 ± 5.0</td>
<td>2.2 ± 2.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Gastric bypass</td>
<td>4.2 ± 6.9</td>
<td>2.7 ± 3.0</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

*Includes appendectomy, cholecystectomy, antireflux surgery, and gastric bypass.

²χ², Fisher exact test, or Student t tests, where applicable.

×Includes appendectomy and cholecystectomy only.
procedures. As shown in Table 2, 92,490 patients (67%) had laparoscopic surgery and 46,105 patients underwent open surgery. The proportion of females was higher in the laparoscopic group (67% vs. 48%, \( P < 0.01 \)), as was the proportion of patients with a “minor severity of illness” level (59% vs. 49%, \( P < 0.01 \)). The age distribution was highest for patients grouped between 31 and 50 years (42% for laparoscopic and 38% for open). The proportion of white was higher for the laparoscopic group whereas the proportion of African Americans was higher in the open group. The length of stay was significantly shorter for laparoscopic operations compared with open operations for all 4 procedures.

Overall, VTE was diagnosed during the index hospitalization in 259 of 92,490 (0.28%) laparoscopic cases and 271 of 46,105 (0.59%) open cases (Fig. 1). Univariate analysis showed that open surgery was a significant factor for development of VTE even when stratified according to different level of severity of illness; for minor/moderate severity of illness level the OR was 1.83 (95% CI: 1.32–2.54) and for major/extreme severity of illness level the OR was 1.31 (95% CI: 1.06–1.62). The incidence of VTE after laparoscopic and open appendectomy is listed in Figure 2. Laparoscopic appendectomy was associated with a lower rate of VTE compared with open appendectomy (0.11% vs. 0.28%, \( P < 0.01 \)); however, the association did not persist when the analysis was performed according to different level of severity of illness. The incidence of VTE after laparoscopic and open cholecystectomy is listed in Figure 3. Laparoscopic cholecys-

---

**FIGURE 1.** Overall incidence of VTE in patients who underwent open versus laparoscopic appendectomy, cholecystectomy, antireflux surgery, and gastric bypass operations, and stratified by severity of illness level, 2000–2006. *\( P < 0.01 \); odds ratio (95% confidence interval) for overall group was 2.09 (95% CI: 1.76–2.49), for minor/moderate severity of illness level the OR was 1.83 (95% CI: 1.32–2.54), and for major/extreme severity of illness level the OR was 1.31 (95% CI: 1.06–1.62).

**FIGURE 2.** Incidence of VTE in patients who underwent open versus laparoscopic appendectomy, overall, and by severity of illness level, 2002–2006. *\( P < 0.05 \); odds ratio (95% confidence interval) for appendectomy group was 2.44 (95% CI: 1.54–3.87), for minor/moderate severity of illness level the OR was 1.79 (95% CI: 0.82–3.97), and for major/extreme severity of illness level the OR was 1.60 (95% CI: 0.89–2.90).

**FIGURE 3.** Incidence of VTE in patients who underwent open versus laparoscopic cholecystectomy, overall, and by severity of illness level, 2002–2006. *\( P < 0.01 \); odds ratio (95% confidence interval) for cholecystectomy group was 2.89 (95% CI: 2.31–3.56), for minor/moderate severity of illness level the OR was 1.99 (95% CI: 1.20–3.27), and for major/extreme severity of illness level the OR was 1.35 (95% CI: 1.04–1.74).

**FIGURE 4.** Incidence of VTE in patients who underwent open versus laparoscopic antireflux surgery, overall, and by severity of illness level, 2004–2006. *\( P < 0.01 \); odds ratio (95% confidence interval) for antireflux surgery group was 11.78 (95% CI: 1.86–92.66), for minor/moderate severity of illness level the OR was 24.66 (95% CI: 2.61–580.87), and for major/extreme severity of illness level the OR was 0.0 (95% CI: 0–24.88).
The relative risk of VTE after laparoscopic surgery compared with open surgery is unknown. Certain investigators suggest that the risk for venous thrombosis and PE after laparoscopic surgery may be higher than after open surgery because of the intraoperative use of pneumoperitoneum with its effects on femoral venous flow.6 To date, there have been no large studies examining the incidence of VTE after laparoscopic compared with open surgery.7,8 In this study, we used the UHC Clinical Database to analyze the incidence of VTE in a large cohort of patients who underwent laparoscopic compared with open appendectomy, cholecystectomy, antireflux surgery, and Roux-en-Y gastric bypass. These 4 gastrointestinal procedures were selected because of the availability of ICD-9 codes for open and laparoscopic procedures. We found an overall lower incidence of VTE after laparoscopic compared with open procedures (0.28% vs. 0.59%, respectively). Although there are differences in the severity of illness level between the 2 groups, the incidence of VTE after laparoscopic surgery continues to be lower than that of open surgery even when the data are stratified according to the level of severity of illness. On examination of each of the 4 specific operations, the incidence of VTE is again lower after the laparoscopic operation compared with the open operation, although these differences were not significant for appendectomy. We conclude from this study that laparoscopic operation is associated with a lower incidence of VTE compared with open operation and that laparoscopy in itself should not be viewed as an additional risk factor during risk assessment for venous thrombosis.

Factors predisposing to VTE during open surgical procedure include deficiency of Antithrombin III, protein C and S, and dysfibrinogenemia. Other risk factors include advanced age, obesity, previous history of VTE, cancer, lengthy operation (>2 hours) and immobility.9 In addition, laparoscopic procedures have additional risk factors for development of VTE, which include the use of pneumoperitoneum, reverse Trendelenburg position, and possibly a prolonged operative time during the learning curve of the procedure. Consideration of these possible risk factors has led some investigators to hypothesize that patients undergoing laparoscopic surgery may be at higher risk for development of VTE compared with open surgery.10,11 Results from our study, however, do not support this hypothesis. Ours result conclusively show that laparoscopic surgery is not associated with a higher incidence of clinically symptomatic venous thrombosis or PE compared with open surgery during the hospitalization. In fact, comparison of the 2 groups even after risk adjustment showed that the odds of development of an inpatient VTE is 1.8 times higher after open operation compared with laparoscopic operation.

The findings from our study can be used by surgeons to assess more accurately the individual patient’s risk for perioperative VTE. A common risk assessment method has been reported by Caprini.9 In this risk assessment model, Caprini stratified the patients into 4 categories, low, moderate, high, and highest, based on multiple factors. One of the listed risk factors is laparoscopic surgery (>45 minutes), which receive 2 points. Our study examined antireflux surgery and Roux-en-Y gastric bypass, which normally have an operative time longer than 45 minutes. Despite the longer operative time, laparoscopic gastric bypass and antireflux surgery were associated with a lower incidence of VTE. According to Caprini thrombosis risk factor assessment,9 a hypothetical case study of a 39-year-old morbidly obese female undergoing

**DISCUSSION**

**FIGURE 5.** Incidence of VTE in patients who underwent open versus laparoscopic gastric bypass, overall, and by severity of illness level, 2004–2006. *P < 0.01; odds ratio (95% confidence interval) for gastric bypass group was 2.58 (95% CI: 1.68–3.94), for minor/moderate severity of illness level the OR was 3.37 (95% CI: 1.76–6.45), and for major/extreme severity of illness level the OR was 0.87 (95% CI: 0.48–1.58).
open gastric bypass would have a minimum risk factor score of 3 (1 for obesity and 2 for major surgery) whereas the same patient undergoing laparoscopic gastric bypass would have a minimum risk factor score of 5 (1 for obesity, 2 for major surgery, and 2 for laparoscopic surgery >45 minutes). Our study does not support the use of additional points for laparoscopy during the calculation of thrombosis assessment.

Our conclusions are in agreement with a large clinical series of open and laparoscopic gastric bypass (Table 3), which showed that the incidence of VTE seems to be lower after laparoscopic compared with open gastric bypass (0.5% vs. 1.0%). In a series of 380 patients who underwent laparoscopic gastric bypass without the use of anticoagulant prophylaxis, Gonzalez et al reported a 0.3% incidence of clinically evident deep venous thrombosis.

We recognize that the limitations of data from administrative databases are the accuracy in coding and input of data. Nevertheless, VTE as represented by symptomatic venous thrombosis and/or PE is likely to be an accurate end point because this data point does not require subjective evaluation. Another weakness in comparing the outcome of laparoscopic versus open procedure is the limited use of risk-adjustment in most databases. An argument against the validity of our results is that open procedures were performed in higher risk patients with more comorbidity. Risk adjustment is the key for establishing a valid comparison between laparoscopic versus open procedures. The UHC database uses an extensive risk adjustment model and methodology to assign a severity of illness level. In our study, the rates of VTE between laparoscopic and open procedures were calculated according to severity of illness level. Within the subgroup analysis according to severity of illness level, the incidence of VTE continues to be lower after laparoscopic operation compared with open operation. Another limitation is that the data used in this study were obtained from an administrative database that does not have any information concerning the use or nonuse of thromboprophylaxis or the type and duration of the prophylaxis. Could it be that our finding of a lower incidence of VTE after laparoscopic surgery stems from the fact that a more aggressive VTE prophylaxis regimen is being used in this patient population? This is unlikely as the current guideline from SAGES states that the same thromboprophylaxis recommendations for open procedures should be followed when the same procedures are accomplished via laparoscopy. There is also lack of information about the physiologic status of the patient and history for venous thrombosis or PE, and lack of body mass index for risk stratification in the morbidly obese patients. Additionally, the UHC database is compiled from discharge abstract data and is limited to in-hospital morbidity only without follow-up data. Therefore, VTE arising after discharge would not be captured in this database and we do not know the true incidence of VTE at follow-up for both groups. White et al showed, in an analysis of 1,653,275 cases using a large administrative database, that 56% of all VTE events were diagnosed after discharge from the hospital. Finally, the more extensive ambulation and earlier discharge after laparoscopic operations may be a major contributing factor for the lower incidence of VTE in the laparoscopic group. However, we theorize that the short differential in the length of stay (<2 days) did not fully explain the large differences in VTE rate between the 2 groups. For example, although the length of stay in the open antireflux surgery group was only 1.7 days longer than the laparoscopic group, the incidence of VTE was 10-fold higher in the open group (1.1% vs. 0.1%, respectively). Similarly, the length of stay in open gastric bypass was only 1.5 days longer than the laparoscopic group, whereas the incidence of VTE was almost 3-fold higher in the open group (0.8% vs. 0.3%, respectively). Nevertheless, whatever the reason, the observation of a decreased association of VTE with laparoscopic compared with open operations remains. Recognizing these limitations, this analysis of a large sample size is the first to demonstrate that laparoscopic surgery is associated with a significantly lower incidence of VTE compared with open surgery.

**CONCLUSIONS**

This study used a large administrative data set to determine the incidence of VTE after 4 commonly performed laparoscopic and open gastrointestinal operations. Overall, the incidence of VTE is lower after laparoscopic operations compared with open operations, even when stratified according to level of severity of illness. Compared with laparoscopic procedures, we found that open procedures were a significant risk factor for development of VTE. The results from this study will help surgeons to appropriately estimate the risk of VTE associated with various laparoscopic operations and implementation of a thromboprophylaxis regimen accordingly.

**TABLE 3. Incidence of VTE After Open Versus Laparoscopic Gastric Bypass From Selected Large Series With More Than 300 Operations**

<table>
<thead>
<tr>
<th>Open Gastric Bypass</th>
<th>No. DVT and PE (%)</th>
<th>Laparoscopic Gastric Bypass</th>
<th>No. DVT and PE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capella and Capella (n = 652)</td>
<td>2 (0.3)</td>
<td>Shikora et al (n = 750)</td>
<td>5 (0.7)</td>
</tr>
<tr>
<td>Obeid et al (n = 925)</td>
<td>14 (1.5)</td>
<td>Biertho et al (n = 456)</td>
<td>4 (0.9)</td>
</tr>
<tr>
<td>Livingston et al (n = 1067)</td>
<td>9 (0.8)</td>
<td>Gonzalez et al (n = 380)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Smith et al (n = 451)</td>
<td>7 (1.6)</td>
<td>Smith et al (n = 328)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Total (n = 3095)</td>
<td>32 (1.0)</td>
<td>Total (n = 3414)</td>
<td>17 (0.5)</td>
</tr>
</tbody>
</table>

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REFERENCES


Substantial Intentional Weight Loss and Mortality in the Severely Obese

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Objective: To compare all-cause mortality in a surgical weight loss cohort with a similarly aged, obese population-based cohort.

Summary Background Data: Significant weight loss following bariatric surgery improves the comorbidities associated with obesity. Improved survival as a result of surgical weight loss has yet to be clearly demonstrated using clinical data.

Methods: The surgical weight loss cohort was a series of consecutive patients treated with a laparoscopic adjustable gastric band in Melbourne between June 1994 and April 2005. The Melbourne Collaborative Cohort Study (MCCS) provided a community control cohort, recruited between 1992 and 1994 and followed to June 2005 to determine vital status. Height and weight were recorded at baseline in both studies. Subjects between 37 and 70 years and with a body mass index (BMI) of ≥35 were included. Vital status was determined by follow-up and searching of death registries. Survival time was compared using Kaplan-Meier estimates, and hazard of death was determined using Cox regression, adjusting for sex, age at baseline, and BMI at baseline.

Results: Of 966 weight loss patients (mean age 47 years, mean BMI 45 kg/m²), the median follow-up time was 4 years. Mean weight loss after 2 years was 22.8% (58% of excess weight). The MCCS cohort included 2119 severely obese members (mean age, 55 years; mean BMI, 38 kg/m²; median follow-up time, 12 years). There were 4 deaths in the weight loss cohort and 225 deaths in the MCCS cohort. Weight loss patients had 72% lower hazard of death than the community control cohort (hazard ratio, 0.28; 95% confidence interval, 0.10 – 0.85).

Conclusions: Substantial surgical weight loss in a morbidly obese population was associated with a significant survival advantage.


Obesity is increasing in prevalence worldwide. In the United States, it is estimated that 32% of the adult population (approximately 60 million people) are now obese.1 Obesity is associated with higher rates of death from all causes among both men and women in all age groups and now represents one of the major causes of preventable death.2–4 The risk is most evident in younger and middle-aged men and women.5

It still remains to be determined, however, whether significant weight loss reduces the risk of death associated with obesity. Several large epidemiological studies6–13 have shown that unintentional weight loss in adults with or without obesity is generally associated with decreased survival. In these studies, it has been assumed that underlying disease is the cause of death. Conversely, intentional weight loss has been associated with either no change or possibly a reduced risk of death.6,8,9 In these studies, it has been difficult to assess the intentionality of the weight loss.8 The potential benefit of even a modest weight loss was demonstrated by Wannamethee et al,13 who performed a prospective study of 4869 men, aged 56 to 75 years, who completed a questionnaire about intentional and unintentional weight loss over the preceding 4 years and were then followed up for 7 years. Those who stated that they lost weight intentionally had a mortality rate almost half that of those who reported no weight change. This survival benefit was most apparent in those who were initially overweight [body mass index (BMI) >28].

Intentional weight loss as a result of bariatric surgery should be a powerful model to study the effect of weight loss on survival because patients undergoing these procedures are usually severely obese, are intent on weight loss, and can be expected to lose a substantial amount of weight and maintain that weight loss over many years. Two studies have reported a survival advantage for bariatric surgical patients.14–16 However, the accuracy of the survival estimate from each of the studies can be questioned, as their control groups were...
derived from populations already under medical care or were not matched in other ways to the operated cohort. Christou et al.\textsuperscript{14,15} compared a cohort of 1035 patients who had undergone bariatric surgery with a group of 5746 morbidly obese patients, matched for age and sex, who had been treated within the Quebec healthcare system. They showed a major difference in mortality risk (0.68\% in the surgical weight loss group compared with 6.17\% in the control group (relative risk 0.11; 95\% confidence interval (CI), 0.04 – 0.27). Flum and Dellinger\textsuperscript{16} evaluated short and long-term mortality in all patients undergoing gastric bypass surgery in the state of Washington between 1987 and 2001 and compared the survival of those alive at 1 year after operation with a group of obese people derived from a statewide hospital discharge database. The adjusted hazard ratio for the weight loss group was 0.67 (95\% CI 0.54 – 0.85, ie, 33\% higher survival compared with the nonoperated control group). This study used administrative codes rather than clinical parameters to derive the comparative cohort and was unable to consider hospitalized obese patients. The Swedish Obese Subjects Study was a 2-cohort, matched comparative study comparing patients who had a mix of surgical weight loss interventions and a nonsurgically managed group of obese patients. The 10-year follow-up of this study indicated marked improvements in cardiovascular risk factors and diabetes, but too few patients had completed follow-up to analyze data on survival.\textsuperscript{17}

The purpose of the present study was to compare rates of all-cause mortality for a group of obese people in the general community with a group of obese patients who underwent placement of a laparoscopic adjustable gastric band (LAGB). We hypothesized that patients undergoing significant and sustained weight loss through adjustable gastric banding would have a lower risk of death compared with a cohort of obese subjects drawn from the community at large.

**METHODS**

**Study Design**

This was an observational 2-cohort study comparing a group of patients who underwent LAGB placement to a previously established population-based cohort (referred to hereafter as the community control cohort). For comparability between cohorts, we selected individuals from each cohort who at baseline were aged between 37 and 70 years and had a BMI of 35 kg/m\(^2\) or greater.

**Study Population**

**Weight Loss Cohort**

The weight loss cohort represented consecutive patients with severe obesity treated by placement of a LAGB (LAGBAND, Allergen Health, Irvine, CA). All patients were treated in a single clinic in Melbourne, Australia, between January 1993 and April 2005. Eligibility criteria for weight loss surgery through this clinic included BMI \(\geq 35\), a history of multiple attempts to lose weight over the prior 5 years, and medical, physical, or psychosocial problems associated with obesity. For this analysis, we excluded those patients who had had previous weight loss surgery, as it rendered their initial BMI incomparable with the control cohort. Before surgery, patients in this clinic consulted with a surgeon, completed questionnaires regarding their demographic characteristics, medical history, and general well-being, and underwent a medical examination. Following placement of the LAGB, all patients were encouraged to continue to attend the clinic, frequently at first but at least once a year thereafter for ongoing clinical assessment and when appropriate for adjustment of the settings of the band by addition or removal of saline. All patient data were maintained on a computerized database (LapBase, LapBase Systems, Melbourne). All patients were informed of the procedure and follow-up protocol and gave written consent. The use of de-identified information from this database for the present study was approved by the ethics committee of The Avenue Hospital.

There were 966 patients operated on since January 1993 who fulfilled all the inclusion criteria for the current study. Of these 966, 45 (4.7\%) had had the LAGB removed during follow-up. Mean weight loss in the 84\% with weight recorded after 2 years was 28.6 kg (standard deviation 14.6 kg), which equates to 22.6\% (standard deviation 9.5\%). Mean weight loss in the 37\% with weight recorded after 5 years was 27.0 kg (standard deviation 14.3 kg), which equates to 21.9\% (standard deviation 10.1\%).

**Community Control Cohort: The Melbourne Collaborative Cohort Study**

The Melbourne Collaborative Cohort Study (MCCS) is a prospective cohort study of 41,528 people (17,049 men) aged between 27 and 75 years at baseline (99.3\% were aged 40 – 69 years). Details of the MCCS have been published elsewhere.\textsuperscript{18} Recruitment to the MCCS occurred between 1990 and 1994. Subjects were recruited via the Electoral Rolls (registration to vote is compulsory for Australian adults), advertisements, and community announcements. The study aimed to explore associations between certain epidemiological factors such as diet, body size, and behavior and cancer. Southern European migrants to Australia were deliberately oversampled to extend the range of lifestyle exposures and to increase genetic variation. The Cancer Council Victoria’s Human Research Ethics Committee approved the study protocol. Subjects gave written consent to participate and for the investigators to obtain access to their medical records. For the current analysis, subjects were excluded if they fell outside the specified age and BMI ranges. There were 2119 MCCS participants who fulfilled the eligibility criteria for the current study.

**Data Collection**

**Height and Weight**

In both cohorts, data were recorded in face to face interviews at baseline. Demographic information was collected through questionnaires. Height and weight were measured once at baseline attendance for each participant according to written protocols that were based on standard procedures.\textsuperscript{19} Weight was measured to 100 g using digital electronic scales, and height to 1 mm using a stadiometer. Baseline BMI was calculated as weight/height\(^2\) (kg/m\(^2\)).
Mortality Follow-up

Weight Loss Cohort: The vital status of the 966 surgical patients was confirmed between April 2004 and April 2005. Confirmation for the majority was through their annual follow-up visits to the clinic. Those who did not present within the year were telephoned to confirm vital status. A search of all public listings of telephone and address information was used to identify additional patients. At the end of this process, we were unable to contact 23 (2.4%) of the eligible patients. The identifying details of these participants were submitted to the Victorian Registry of Births, Deaths and Marriages for matching. None of the 23 was found on their death records. We have included these 23 in the analyses, using their follow-up time until their last reported visit and then considering them censored.

The Melbourne Collaborative Cohort Study: Deaths in the community cohort were identified through the Victorian Registry of Births, Deaths and Marriages, and the National Death Index. Recording of deaths was complete to June 2005. Residential addresses were determined by record linkage to Electoral Rolls, from electronic phone books and from responses to mailed questionnaires and newsletters. Of the 2119 participants used in this analysis, 3 were known to have left Australia, and were considered lost to follow-up in this analysis.

Statistical Analysis

Participants in the 2 cohorts were compared with respect to gender, age at baseline, BMI at baseline and follow-up time since baseline using standard hypothesis tests for proportions, means or medians.

Crude survival was determined for the 2 cohorts, for the total population and within subgroups defined by sex, age, and baseline BMI. Survival was analyzed using crude all-cause mortality rates and Kaplan-Meier survival plots. The expected number of deaths in the weight loss cohort was estimated using sex-, age-, and BMI-standardized mortality rates based on the community control cohort’s rates by sex, age group throughout follow-up (37–49, 50–64, 65–74, >75), and BMI group (35–39, >40).

Cox proportional hazards regression models, using time in study as the time scale, were used to estimate the hazard ratios associated with weight loss after adjustment for confounding variables. The models were adjusted for age at baseline (continuous), sex, and baseline BMI (continuous). Quadratic terms for age and BMI were tested but did not improve the models or affect the hazard ratio associated with the weight loss cohort, so they were not included in the final models. According to analysis of the Schoenfeld residuals,20,21 the assumption of proportional hazards was not violated for any of the variables in this model. Exploratory analyses were also performed to examine variation in the hazard ratio for weight loss according to age, sex, or BMI. Variation was explored through subgroup analyses and the fitting of interaction terms between cohort and age, sex, or BMI (both as a continuous variable and as a categorical variable of BMI below or above 40) and entering them separately into the Cox model. Because of the differences in follow-up times between the 2 cohorts, Cox regressions were also performed using follow-up times censored at 5 and 10 years.

Statistical significance was set at the 5% level for all analyses. All analyses were performed using Stata/SE 8.0 (Stata Corporation, College Station, TX).

RESULTS

The 2 cohorts were similar with respect to gender (Table 1). Those from the community control cohort (MCCS) were older and had lower BMIs. Median follow-up was longer within the community control cohort (ranging from 5 months to 14.6 years) than within the weight loss cohort (ranging from 1 month to 10.8 years).

There were 4 deaths in the weight loss cohort (2 from cancer, 1 from myocardial infarction and 1 from suicide). There were no perioperative deaths. There were 225 deaths in the community control cohort. Crude mortality rates were 8-fold higher in the community control group compared with the weight loss cohort (Table 2, Fig. 1). The mortality reduction associated with the weight loss cohort was greater in men than women and higher in those with a higher initial BMI (Table 2).

From the Cox regression analysis, adjusted for sex, age, and BMI, the hazard for death was around 72% lower in the weight loss cohort (Table 3). There was a consistently decreased hazard of death in the weight loss cohort compared with the community control cohort within all the subgroups analyzed. Although the association was stronger in those with a higher initial BMI (Table 3), interaction terms between sex, age, or BMI and cohort were not significant (P > 0.05). Adjustment for age and BMI in deciles had little effect on the hazard ratio (0.36, 95% CI 0.12-1.05). When the follow-up time was censored at 5 and 10 years, the adjusted hazard ratios for death were 0.18 (95% CI 0.03-0.91) and 0.36 (95% CI 0.12-1.09), respectively. Excluding the first year of follow-up from the analysis had little effect on the mortality hazard ratio.

DISCUSSION

Substantial weight loss in the severely obese was associated with a 72% lower risk of all cause mortality (82% lower at 5 years) in this comparison of a cohort of patients having treatment with LAGB with a community control cohort. The survival difference was apparent in both sexes, different age groups and across a range of initial BMI. The average weight loss in the surgical cohort was 28.6 kg for the 84% who had weight recorded at 2 years after surgery and 27.0 kg for the 37% with weight recorded at 5 years after surgery.

<table>
<thead>
<tr>
<th>TABLE 1.</th>
<th>Demographic Comparison of the Weight Loss and Community Control Cohorts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Community Control Cohort</td>
</tr>
<tr>
<td>N</td>
<td>2119</td>
</tr>
<tr>
<td>% male</td>
<td>22.9</td>
</tr>
<tr>
<td>Age (yr), mean (IQR)*</td>
<td>55.2 (14)</td>
</tr>
<tr>
<td>BMI (kg/m^2), mean (IQR)*</td>
<td>38.3 (3.7)</td>
</tr>
<tr>
<td>FU time (yr), median (IQR)*</td>
<td>12.3 (2.1)</td>
</tr>
</tbody>
</table>

*Denotes a statistically significant difference (P < 0.05) between the 2 cohorts.
TABLE 2. Crude Mortality Differences Between the Weight Loss and Community Control Cohorts

<table>
<thead>
<tr>
<th>Community Control Cohort</th>
<th>Weight Loss Cohort</th>
<th>Expected No. Deaths in the Weight Loss Cohort*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Deaths</td>
<td>225</td>
<td>4</td>
</tr>
<tr>
<td>FU time (1000 person years)</td>
<td>25.0</td>
<td>3.7</td>
</tr>
<tr>
<td>Rate per 1000 person years (95% CI)</td>
<td>8.9 (7.8–10.1)</td>
<td>1.1 (0.4–2.9)</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaths</td>
<td>95</td>
<td>1</td>
</tr>
<tr>
<td>FU time (1000 person years)</td>
<td>5.5</td>
<td>0.7</td>
</tr>
<tr>
<td>Rate per 1000 person years (95% CI)</td>
<td>17.3 (14.1–21.1)</td>
<td>1.4 (0.2–10.0)</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaths</td>
<td>130</td>
<td>3</td>
</tr>
<tr>
<td>FU time (1000 person years)</td>
<td>20.0</td>
<td>3.0</td>
</tr>
<tr>
<td>Rate per 1000 person years (95% CI)</td>
<td>6.6 (5.5–7.8)</td>
<td>1.0 (0.3–3.1)</td>
</tr>
<tr>
<td>Age &lt;50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaths</td>
<td>22</td>
<td>2</td>
</tr>
<tr>
<td>FU time (1000 person years)</td>
<td>7.1</td>
<td>2.6</td>
</tr>
<tr>
<td>Rate per 1000 person years (95% CI)</td>
<td>3.1 (2.1–4.7)</td>
<td>0.8 (0.2–3.0)</td>
</tr>
<tr>
<td>Age ≥50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaths</td>
<td>203</td>
<td>2</td>
</tr>
<tr>
<td>FU time (1000 person years)</td>
<td>18.0</td>
<td>1.1</td>
</tr>
<tr>
<td>Rate per 1000 person years (95% CI)</td>
<td>11.1 (9.7–12.8)</td>
<td>1.8 (0.5–7.2)</td>
</tr>
<tr>
<td>BMI &lt;40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaths</td>
<td>167</td>
<td>2</td>
</tr>
<tr>
<td>FU time (1000 person years)</td>
<td>20.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Rate per 1000 person years (95% CI)</td>
<td>8.5 (7.3–9.9)</td>
<td>1.9 (0.5–7.7)</td>
</tr>
<tr>
<td>BMI ≥40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaths</td>
<td>58</td>
<td>2</td>
</tr>
<tr>
<td>FU time (1000 person years)</td>
<td>5.6</td>
<td>2.7</td>
</tr>
<tr>
<td>Rate per 1000 person years (95% CI)</td>
<td>10.4 (8.0–13.5)</td>
<td>0.7 (0.2–3.0)</td>
</tr>
</tbody>
</table>

*Based on sex, age, and BMI-standardized mortality rates from the community control cohort.
FU indicates follow-up.

FIGURE 1. Kaplan-Meier survival estimates in the weight loss and community control cohorts.
There was a suggestion that the hazard ratio for mortality associated with weight loss differed according to age, sex, and initial BMI, but tests for interaction with these variables were not significant. With so few events in each subgroup in this study, it will be important to follow-up these findings in future studies to see whether men and those with more severe obesity have a greater relative potential to benefit from substantial weight loss.

The principal finding of the present study demonstrated a relative risk of death of 0.28 and supports the findings of Flum and Dellinger10 and Christou et al,14,15 which were 0.67 and 0.11, respectively. The mortality rate per 1000 patient years in our control group was 9 at an average age of 55.2 years compared with 12 for the Quebec study with an average age of 46.7 years. This may reflect the compromised health status of the control group of that study.14,15 Probable explanations for the differences between these findings include their different sources of control groups, and the different surgical procedures involved.

The major limitation of this study is the small number of deaths in the weight loss cohort. This resulted in broad CI for the main effect and an inability to conclude on subgroup analyses. Although we can conclude that LAGB surgery in the morbidly obese patients is associated with a mortality reduction, we cannot be precise about the magnitude of this effect. In addition, the small number of deaths gives added importance to the 23 individuals from the weight loss cohort that were unable to be contacted between April 2004 and April 2005. Searches of the Victorian Registry of Births, Deaths and Marriages did not find any deaths in this group. Without knowing the whereabouts of these individuals, we cannot guarantee that they have not died elsewhere. Scenario analyses indicated that with an additional death in this group, the reduction in mortality would still have been significant at the 5% level, while if all 23 had died, the weight loss group would be associated with an increased mortality risk.

The second major limitation of this study is that it is comparing 2 cohorts that were not originally intended for comparison. Consequently, it was not possible to adjust for other variables that potentially confound the relationship between intentional weight loss and survival, such as education, ethnicity, smoking status, comorbidities, and health insurance. This also led to substantial differences in the median follow-up times of the 2 cohorts. However, analyses performed on the data truncated at different follow-up times resulted in similar hazard ratios to the overall data. Further, we do not have any information on the occurrence of weight loss surgery for members of the community control cohort. Although it is extremely unlikely that a community cohort experienced any major weight loss, any such cases would have biased the result towards no difference, suggesting that our estimate is an underestimate of the true survival advantage. In addition, although both cohorts are assumed to represent the same underlying obese population, both are in their own ways selected: the MCCS with voluntary participation and over-sampling of the Mediterranean population and the weight loss cohort through eligibility for LAGB placement. An analysis comparing the weight loss cohort solely with the Australian born members of the MCCS cohort showed a statistically significant mortality reduction similar to the overall analysis (data not shown). The fact that all the weight loss group participants had private health insurance, and had attempted to lose weight many times before surgery may have biased our results somewhat toward a greater survival advantage in the weight loss cohort. In contrast, the MCCS study sample is known to have a lower mortality rate than the general population, which, if also true for this sample, would bias the results in the other direction.18 The fact that the majority of the weight loss cohort received regular medical attention and advice after LAGB placement means that although we can conclude that LAGB placement under current conditions confers a substantial survival advantage in the severely obese population, future studies of other forms or degrees of weight loss will be required to extrapolate these findings to weight loss in the obese patients in general.

A priority for further research will be to build on the advances made in this study—use of a community control cohort, and adjustment for baseline BMI—using larger populations and matching for key variables. The ideal study remains a randomized controlled trial, with mortality as the primary outcome measure. At a recent International Congress on Obesity, there were 3 reports on surgical weight loss and mortality—all showing a survival advantage associated with weight loss.22–24 However, with 1 based on older surgical techniques,24 1 using self reported BMI22 and 1 using patient controls,23 there is still a need for a comprehensive longitudinal study in this area.

It is well known that obesity is associated with premature mortality,25 and there are a number of mechanisms whereby intentional weight loss, through sustained calorie restriction, is thought to prolong life. Dietary restriction has been shown to slow aging and improve health and longevity in a range of mammals, including primates.26 This effect is likely to be mediated by a host of metabolic and inflammatory mechanisms including reduced insulin levels with improved insulin sensitivity, lower resting metabolic rate, temperature, and blood pressure, lower leptin and higher adiponectin concentrations, more
favorable lipid levels, lower levels of inflammatory markers, and improved endothelial function. All these effects accompany calorie restriction and weight loss in obese humans and provide significant disease improvement or resolution. There is good evidence that modest weight loss through dietary restriction and lifestyle change reduce the risk of developing diseases associated with increased mortality. Although it is assumed that the survival advantages presented here are primarily due to weight loss per se, a priority for future studies with larger numbers of events will be to derive the dose-response relationship of survival and weight loss.

Weight loss therapy is not without risk. There is the potential for nutritional deficiencies, serious adverse events and mortality with surgery, pharmacotherapy, and very low-calorie diets. In our study there was no perioperative or band-related mortality, but the potential for early mortality, or later procedure-related mortality needs to be considered when evaluating any survival advantage.

With continuing controversy regarding the effect on health risk of intentional weight loss, weight loss has not been universally advocated as a beneficial strategy. This study demonstrates that substantial weight loss is associated with prolonged survival. Although there are limitations in comparing 2 observational cohorts derived for separate purposes, these finding suggest a significant reduction in the risk of death that does not seem to be the result of confounding alone. Bariatric surgery is known to improve the quality of life and reduce the burden of comorbid illness for obese patients. Given the plausible causative pathway of weight reduction, comorbidity improvement, and reduced risk of death, this study suggests that weight loss surgery is also a life-prolonging intervention and one that should be encouraged for those with severe obesity.

ACKNOWLEDGMENTS

The authors thank the many participants and research personnel associated with each study cohort.

REFERENCES

Predictive Factors of Outcome After Gastric Banding
A Nationwide Survey on the Role of Center Activity
and Patients’ Behavior

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Michel Marty, MD,‡ Françoise Nogues, MD,‡ Karem Slim, MD,§ and Arnaud Basdevant, MD, PhD¶¶**

Background: Systematic studies of postoperative outcome of bariatric surgery provide information on the predictors of success. Surgeon’s and institution experience and patient’s behavior after surgery are key determinant of success or failure. Data on clinical trials generally reflect the experience of skilled obesity surgery centers. Little is known about the current practice at a nationwide level. The present study was realized in the frame of a national survey on medical and surgical practices conducted by the public health insurance system. The objective was to analyze systematically and prospectively the outcome of all bariatric surgery procedures consecutively performed in a given period, as registered by the French National Medical Insurance Service. This study at a nationwide level focused on predictive factors of success and analyzed how the experience of the centers relates to the patients’ outcomes at 1 and 2 years after surgery.

Methods: This study examined prospectively the 2-year predictors of success of all consecutive 1236 bariatric operations performed at a nationwide level. Most (87.3%) were laparoscopic adjustable gastric banding (LAGB), so that the non-LAGB were eliminated from the study. Data were collected independently by consultants of the French National Medical Insurance Service: characteristics of the patients, evolution of body mass index (BMI), physical activity and comorbidities, changes in behavior, complications, reoperations. Information was available on the activity of the surgical teams. Excess weight loss (EWL) >50% was considered a “success,” and EWL <50% “not a success.” A backstep logistic regression (likelihood ratio test) was used to determine predictive factors.

Results: Statistical analysis showed significant differences in EWL with the following data: age <40 years (P < 0.01), initial BMI <50 kg/m² (P < 0.001), experience of the surgeon(s) >2 procedures per week (P < 0.01), recovery of physical activity (P < 0.001), and change in eating habits (P < 0.001). Compared with 15- to 39-year-old patients, 40- to 49-year-old patients have a 1.5 higher risk not to have a success after surgery and over 50-year-old patients a 1.8 higher risk. Morbidly obese patients (40 < BMI < 49) had a 2.6 times higher risk not to have a success than patients with severe obesity (35 < BMI < 39). Superobese patients (BMI >50) had a 5.4 times higher risk not to succeed than patients with severe obesity. Being operated by a team with a surgical activity over 15 bariatric procedures/2 months doubles the chance of a successful operation when compared with patients operated by surgical teams having only performed 1 or 2 bariatric procedures. Patients who had not recovered or increased their physical activity after operation had a 2.3 times higher risk not to have a success than those who did. Patients who had not changed their eating habits had a 2.2 times higher risk not to have a success than those who did.

Conclusions: This nationwide survey shows that the best profile for a success after gastric banding is a patient <40 years, with an initial BMI <50 kg/m², willing to change his eating habits and to recover or increase his physical activity after surgery and who has been operated by a team usually performing >2 bariatric procedures per week. This study emphasizes that obesity surgery requires a significant experience of the surgical team and a multidisciplinary approach to improve behavioral changes.

(Ann Surg 2007;246:1034–1039)}
cedures in the “real life” and are looking for criteria for qualifying “center of excellence.”

The aim of the present study was to identify the predictive factors of success after gastric banding and the relationship between outcomes and both patients’ characteristics and operative volume of the surgeon.

**METHODS**

This observational study involved all the patients undergoing bariatric surgery in any public or private center from all over France in December 2002 and January 2003 (n = 1238). They were operated in 79 public (nonprofit) and 184 private surgical centers, by 310 different teams. The 1- and 2-year follow-up examinations were performed in March and April 2004 and 2005 by consultants of the French National Medical Insurance Service. Subjects were informed of the aim of the study and gave their consent to participate. All data were collected on a regional basis and collected through a systematic clinical procedure including clinical examination and questionnaires as previously described.4

The present study evaluated the factors that could help to predict success after bariatric surgery. Only the data after laparoscopic adjustable gastric banding (LAGB) could be of interest because of the rate of LAGB in this series (87.3%).

The criterion we chose to identify success after surgery was the “excess weight loss” (EWL) calculated 1 and 2 years after operation: patients with an EWL ≥50% were considered as a success, patients with an EWL <50% as “not a success,” which is different from a failure of the surgery (EWL <20% according to Reinhold). A χ² test was applied to compare this variable and any of the following data that had been collected after 1 and 2 years: age and sex of the patient, initial BMI, specific surgical complications (yes/no), abdominal reoperations due to bariatric surgery (yes/no), postoperative surgical consultation (yes/no), postoperative follow-up by the GP (yes/no), specialization of the referring practitioner, recovery or improvement in physical activity (yes/no), improvement of respiratory comorbidities (yes/no), of cardiovascular comorbidities (yes/no), of joint comorbidities (yes/no), metabolic comorbidities (yes/no), multidisciplinary postoperative follow-up (yes/no), postoperative changes in eating habits, experience of the surgical teams at operative time (activity expressed in quartiles of patients). “Change in eating habits” means that the patient answered positively to the question “did you change quantitatively or qualitatively your eating habits, respect the diet counseling, eat very slowly, tiny bites, etc . . .”.

Data that showed significant differences were used for statistical analysis.

**Logistic Regression**

On the one hand, 15 to 29 and 30- to 39-year-old groups and on the other hand 50 to 59 and 60- to 79-year-old groups were gathered for a logistic regression. The analysis applied to determine predictive factors for surgery was a backstep logistic regression (likelihood ratio test): the odd-ratios of the levels of the variables retained by the backstep regression at the last step of the model were studied according to their statistical level of significance (odd-ratio statistically different from 1).

**RESULTS**

**Univariate Analysis (Table 1)**

The χ² test showed significant differences between the variable indicator of success after surgery (EWL >50%) and those 5 following factors (Table 1):

- **Age of the patient:** 15- to 39-year-old group showed better results than 40 to 49 years and over 50-year-old groups (P < 0.01)
- **Initial body mass index (BMI):** severe obesity group (35 < BMI < 39) had better results than morbid obesity group (40 < BMI < 49) and superobesity group (BMI >50) (P < 0.001)
- **Recovery of physical activity (P < 0.001)**
- **Surgical activity:** groups of teams having performed more than 6 bariatric surgery in 2 months (7–14 and more than 14) had better results than surgical teams having operated less (1–2, or 3–6) (P < 0.01)
- **Change in eating habits (P < 0.001)**

**Multivariate Analysis (Table 2)**

The backstep regression found the same data as step 1. All odd-ratios calculated on modalities of the data are statistically significant (Table 2):

- **Age of the Patients**
  
  Compared with the 15- to 39-year-old patients, the 40- to 49-year-old patients had a 1.5 higher risk not to have a success after surgery and the over 50-year-old patients a 1.8 higher risk.

- **Initial BMI**
  
  The patients suffering from morbid obesity (40 < BMI < 49 kg/m²) had a 2.6 times higher risk not to have a success than those who have severe obesity (35 < BMI < 39). The superobese patients (BMI >50 kg/m²) had a 5.4 times higher risk not to have a success than those who have severe obesity.

- **Recovery or Increase in Physical Activity**
  
  Patients who have not recovered or increased their physical activity after operation have a 2.3 times higher risk not to have a success than those who did.

- **Surgical Volume**
  
  Patients operated by surgical teams having performed >15 bariatric procedures between December 2002 and January 2003 have almost twice as much (×1.9) chance that the operation will be a success (=almost twice as less risk that the operation will not be a success) than those who have been operated by surgical teams having only performed 1 or 2 bariatric procedures. This risk is still 1.7 times higher for the patients operated by teams having done a little more operations (3–6 and 7–14). At 1 year, the EWL according to the number of bariatric procedures performed during the 2-month
TABLE 1. Excess Weight Loss After Gastric Banding According to the Characteristics of Patients

<table>
<thead>
<tr>
<th>Characteristics of Patients</th>
<th>Failure EWL &lt;50%, n (%)</th>
<th>Success EWL ≥50%, n (%)</th>
<th>χ² Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15–39 yrs</td>
<td>274 (59.3)</td>
<td>188 (40.7)</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td>40–49 yrs</td>
<td>186 (67.19)</td>
<td>91 (32.9)</td>
<td></td>
</tr>
<tr>
<td>Above 50 yrs</td>
<td>146 (71.9)</td>
<td>57 (28.1)</td>
<td></td>
</tr>
<tr>
<td>Initial BMI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe obesity (BMI between 35 and 39 kg/m²)</td>
<td>85 (44.5)</td>
<td>106 (55.5)</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Morbid obesity (BMI between 40 and 49/kg/m²)</td>
<td>404 (66.6)</td>
<td>203 (33.4)</td>
<td></td>
</tr>
<tr>
<td>Severe obesity (BMI above 50/kg/m²)</td>
<td>110 (80.9)</td>
<td>26 (19.1)</td>
<td></td>
</tr>
<tr>
<td>Did the patient recover or increase physical activity?</td>
<td></td>
<td></td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Yes</td>
<td>359 (58.0)</td>
<td>260 (42.0)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>231 (76.2)</td>
<td>72 (23.8)</td>
<td></td>
</tr>
<tr>
<td>Surgical volume (/2 mo)</td>
<td></td>
<td></td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td>1–2 interventions</td>
<td>125 (68.7)</td>
<td>57 (31.3)</td>
<td></td>
</tr>
<tr>
<td>3–6 interventions</td>
<td>199 (67.7)</td>
<td>95 (32.3)</td>
<td></td>
</tr>
<tr>
<td>7–14 interventions</td>
<td>168 (67.5)</td>
<td>81 (32.5)</td>
<td></td>
</tr>
<tr>
<td>15 interventions and more</td>
<td>114 (52.5)</td>
<td>103 (47.5)</td>
<td></td>
</tr>
<tr>
<td>Did the patient change eating habits after operation?</td>
<td></td>
<td></td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Yes</td>
<td>525 (62.4)</td>
<td>317 (37.6)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>70 (82.4)</td>
<td>15 (17.6)</td>
<td></td>
</tr>
</tbody>
</table>

TABLE 2. Excess Weight Loss After Gastric Banding According to the Characteristics of Patients/Logistic Regression: Odds Ratios

<table>
<thead>
<tr>
<th>Characteristics of Patients</th>
<th>Significance</th>
<th>Odds Ratios</th>
<th>Confidence Bounds for Odds Ratios</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15–39 yrs</td>
<td></td>
<td>1.500</td>
<td>1.072 2.100</td>
</tr>
<tr>
<td>40–49 yrs</td>
<td>0.018</td>
<td>1.884</td>
<td>1.277 2.779</td>
</tr>
<tr>
<td>Above 50 yrs</td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial BMI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe obesity (BMI between 35 and 39 kg/m²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morbid obesity (BMI between 40 and 49/kg/m²)</td>
<td>0.000 2.649</td>
<td>1.860 3.773</td>
<td></td>
</tr>
<tr>
<td>Severe obesity (BMI above 50/kg/m²)</td>
<td>0.000 5.367</td>
<td>3.145 9.159</td>
<td></td>
</tr>
<tr>
<td>Did the patient recover or increase physical activity?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td>2.347</td>
<td>1.691 3.257</td>
</tr>
<tr>
<td>No</td>
<td>0.000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical volume (/2 mo)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–2 interventions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3–6 interventions</td>
<td>0.006</td>
<td>1.864</td>
<td>1.200 2.895</td>
</tr>
<tr>
<td>7–14 interventions</td>
<td>0.008</td>
<td>1.703</td>
<td>1.153 2.516</td>
</tr>
<tr>
<td>15 interventions and more</td>
<td>0.010</td>
<td>1.702</td>
<td>1.133 2.557</td>
</tr>
<tr>
<td>Did the patient change eating habits after operation?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0.009</td>
<td>2.244</td>
<td>1.228 4.099</td>
</tr>
</tbody>
</table>

(Reference) indicates class of the variable chosen to be compared with others classes.
period is shown in Table 3 and Figure 1: significantly better results were obtained when more than 15 procedures have been done (P (ANOVA) < 0.001).

### Change in Eating Habits
Patients who have not changed their eating habits have a 2.2 times higher risk not to have a success than those who did.

### Specific Complications After Gastric Banding
Specific complications after LAGB have been previously reported after 1- and 2-year follow-up. Among the 1083 patients followed after 1 year, 946 underwent a LAGB. One hundred sixty-one patients had 196 complications directly related to the LAGB: 89 port problems (9.4%), 48 slippages (5.1%), 15 acute pouch dilatations (1.6%), 12 gastric erosions (1.3%), 8 esophageal dilatations (0.9%), 7 diet intolerances (0.8%), 6 band infections (0.6%), 5 hemorrhages (0.5%), 3 gastric perforations or necrosis (0.3%), and 3 digestive perforations (0.3%). Fifty-one patients have been reoperated (5.4%) and 22 bands have been removed (2.3%). Table 3 and Figure 1 show a significant lower rate of specific complications after LAGB when >15 procedures have been done during the 2-month period: from >20% to <9% (P χ² < 0.01).

### DISCUSSION
It appears clearly in this study (Table 3, Fig. 1) that if the surgical team has performed >15 procedures during this 2-month period (=2 bariatric procedures per week), the patients have almost twice as much chance to have a success than if only 1 procedure is done per month, and that the rate of specific complications will be <10% at 1 year. Bariatric surgery is a new specialization due to an emerging public health problem. Many studies have tried to determine data on the learning curve. This has been mainly emphasized specifically for gastric bypass, but is also worthwhile for LAGB. For Lord et al, the learning curve in obesity surgery is 50 patients, with additional periods of postgraduate workshops. Shapiro et al showed a significant difference in operative time, complication, and reoperation rates between the first 30 patients and the second 30 patients, independently from the surgeon’s history of advanced laparoscopic experience. We have previously reported an important fall of slippage rate after 5 years experience of band placement. The strength of this study is that it is not the experience of a skilled obesity surgery center but the “real life” at a nationwide level. Current practice compared favorably with published clinical trials. However, good results in experienced surgical centers do not mean only skilled surgeons; they are mainly related to the volume and to a multidisciplinary approach with preoperative preparation and well-organized follow-up. It means that obesity surgery should be performed in “Reference obesity centers.”

Some patients’ characteristics can be predictive factors of success after banding. This study shows a determinant significance of the age of the patient. Compared with patients under 40, patients older than 40 have a 1.5 times higher risk not to have a success and patients older than 50 a 1.8 higher risk. The predictive role of the age has been settled elsewhere but not often. Busetto et al found that an age under 40 years was a significant success predictor at 1 and 3 years; for Dixon and O’Brien, young age and immaturity were considered as failure predictors. For others no difference could be found between adolescents and adults. Actually LAGB, because of its efficiency and safety, may be performed on 3 digestive perforations (0.3%). Fifty-one patients have been reoperated (5.4%) and 22 bands have been removed (2.3%). Table 3 and Figure 1 show a significant lower rate of specific complications after LAGB when >15 procedures have been done during the 2-month period: from >20% to <9% (P χ² < 0.01).

### FIGURE 1
One-year of follow-up/gastric banding. Percentage of specific complications according to the number of initial interventions (12 months) performed by each surgical team.

### TABLE 3. Gastric Banding at 1 Year: Mean Excess Weight Loss/Mean % of Specific Complications

<table>
<thead>
<tr>
<th>Surgical Volume (Initial Interventions/2 mo)</th>
<th>n</th>
<th>Mean EWL (%)</th>
<th>P (ANOVA)</th>
<th>Complications (No. Patients)</th>
<th>% of Specific Complications</th>
<th>P (χ²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–2 interventions</td>
<td>191</td>
<td>42</td>
<td>&lt;0.001</td>
<td>39</td>
<td>20.3</td>
<td>0.01</td>
</tr>
<tr>
<td>3–6 interventions</td>
<td>306</td>
<td>42</td>
<td></td>
<td>60</td>
<td>19.9</td>
<td></td>
</tr>
<tr>
<td>7–14 interventions</td>
<td>235</td>
<td>40</td>
<td></td>
<td>43</td>
<td>18.3</td>
<td></td>
</tr>
<tr>
<td>15 interventions and more</td>
<td>214</td>
<td>48</td>
<td></td>
<td>19</td>
<td>8.9</td>
<td></td>
</tr>
</tbody>
</table>

FIGURE 1. One-year of follow-up/gastric banding. Percentage of specific complications according to the number of initial interventions (1/2 months) performed by each surgical team.
adolescents, if referred to specialized centers, participating in a central database or registry.\textsuperscript{14}

This work shows that the higher the BMI, the higher the risk of failure after LAGB. In 2002, respective indications between LAGB and gastric bypass (GB) were not very clear. At that time in France, most procedures were restrictive like LAGB (946 of 1083 = 87.3\% in this series), or vertical banded gastroplasty (VBG) (93 of 1083 = 8.6\%). Many studies have already showed that \(< 50\%\) EWL and that was maintained at 3.4 and 5 years. It suggested that, according to its relative safety, LAGB should be recommended as a valid surgical approach for these difficult patients. Myers et al\textsuperscript{17} reported same results on 53 massive superobese patients with a mean BMI of 66 kg/m\(^2\) with an EWL of 43\% after 18 months of follow-up.

Some studies compared LAGB with gastric bypass: they all showed better results after bypass. Biertho et al\textsuperscript{18} compared a series of 456 GB with a series of 805 LAGB. At 18 months, the EWL was 74.6\% for GB versus 40.4\% for LAGB: EWL was statistically superior in the GB group for any BMI ranges. Recently, Bowne et al\textsuperscript{19} reported that GB is superior to LAGB in supermorbidty obese patients: on a prospective comparative analysis of 106 patients with BMI >50 kg/m\(^2\), he found significantly more late complications, reoperations, and less EWL in the LAGB group. Mognot et al\textsuperscript{20} confirmed that, when comparing 179 LAGB and 111 GB on superobese patients, EWL was better after GB (73\% vs. 46\% at 2 years), but with a higher early complication rate (10\% vs. 2.8\%).

The most frequent predictive factor of failure after LAGB was BMI over 50 kg/m\(^2\):\textsuperscript{21} In our experience,\textsuperscript{22} among 1227 obese patients operated since 1996, 39 of 57 superobese still had a EWL beneath 20\% after 5 years. We found 2 reasons for this failure: nonrespect of dietetic rules and/or no surveillance.

Our statistical analysis actually shows that 2 postoperative conditions are determinant to have a success with a LAGB: recovery of a physical activity and change in eating habits. In the Swedish Obese Subjects study,\textsuperscript{1} the fraction of the subjects physically active during leisure time was higher in the surgery group over the 10-year period and the fraction of those physically active during work was higher in the surgery group for the first 6 years of the intervention. It seems to be essential to encourage the patient to continue their weight loss after surgery by beginning sport or gym activities as soon as possible. It will also allow the patient to better accept the excess of skin due to weight loss.

Most of the series have emphasized the important requirement of accompanying the band placement with a considerable change in eating habits. Gastric banding is a restrictive procedure; eating too much will cause the patient to either vomit or dilate the pouch, which can rapidly lead to a pouch dilatation and a band slippage. The evaluation of the compliance to diet counseling was rather crude; however, acknowledging no change in eating habits is most likely to reflect a real lack of compliance. Our data emphasize that compliance to diet counseling is a predictor of success. These results are in keeping with our previous report showing that the 2 main reasons of failure were that the patients did not follow the dietetic rules and/or did not come back for the required follow-up.\textsuperscript{23} Weiner et al\textsuperscript{24} reported outcomes after an 8-year experience of LAGB: quality of life indices improved in 82\% of the first 100 patients. Worse results have been published by Suter et al\textsuperscript{25}: among 317 LAGB performed between 1997 and 2003, 33.1\% developed late complications, mean EWL at 5 years was 58.5\% with the band still in place, but each year added 3\% to 4\% to the major complication rate and the 7-year success rate was only 43\%.

Even if the patient’s characteristics are major predictive factors of success after banding, the present study also shows that the surgical volume parameter is the key predictive factor, independent of the patient’s characteristics. This important finding, both with those significant factors of success (recovery of physical activity and change in eating habits) emphasize that a multidisciplinary team is absolutely required before and after the operation. It is mandatory to prepare the patient by dietetic and psychologic meetings, then to follow him postoperatively to check whether the rules are followed and that physical activity is recovered. This explains the determinant role of the experience of bariatric centers of excellence.

The main limitation of our study is that it reports short-term results. Long-term results cannot be predicted because of the lack of a longer follow-up. Gastric bypasses are nowadays more frequently performed, which can surely be explained by the failures of banding due to insufficient respect of dietetic rules: we can hope that these predictive factors of failure could help to choose the proper first procedure to avoid difficult reoperations like conversion of LAGB to gastric bypass.\textsuperscript{26}

This nationwide statistical study makes it, then, possible to define a typical profile of the patient who will have good weight loss success through gastric banding and define those who will better qualify for a malabsorptive or a mixed procedure. The typical profile of a patient who will succeed with a LAGB is a young patient (under 40 years old), either a man or a woman, with an initial BMI below 50 kg/m\(^2\), well prepared and willing to change his eating habits and well followed, willing to recover a physical activity. To have accurate preparation and surveillance, it is advisable to perform obesity surgery in experienced so-called “reference or excellence obesity centers,” where more than 2 bariatric procedures are performed each week with a multidisciplinary team. These last data are predictive independently from the patient’s characteristics.

REFERENCES


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Prognostic Significance of Multiple Molecular Markers for Patients With Stage II Colorectal Cancer Undergoing Curative Resection

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Objective: The aim of this study was to determine whether our constructed high-sensitivity colorimetric membrane-array method could detect circulating tumor cells (CTCs) in the peripheral blood of stage II colorectal cancer (CRC) patients and so identify a subgroup of patients who are at high risk for relapse.

Summary Background Data: Adjuvant chemotherapy is not routinely recommended in patients diagnosed with UICC stage II CRC. However, up to 30% of patients with stage II disease relapse within 5 years of surgery from recurrent or metastatic disease. The identification of reliable prognostic factors for high-risk stage II CRC patients is imperative.

Methods: Membrane-arrays consisting of a panel of mRNA markers that included human telomerase reverse transcription (hTERT), cytokeratin-19 (CK-19), cytokeratin-20 (CK-20), and carcinoembryonic antigen (CEA) mRNA were used to detect CTCs in the peripheral blood of 194 stage II CRC patients who underwent potentially curative (R0) resection between January 2002 and December 2005. Digoxigenin (DIG)-labeled cDNA were amplified by RT-PCR from the peripheral blood samples, which were then hybridized to the membrane-array. All patients were followed up regularly, and their outcomes were investigated completely.

Results: Overall, 53 of 194 (27.3%) stage II patients were detected with the expression of all 4 mRNA markers using the membrane-array method. After a median follow up of 40 months, 56 of 194 (28.9%) patients with stage II CRC developed curative resection. Postoperatively, relapse was significantly correlated with the expression of all 4 mRNA markers. Combining the expression of all 4 mRNA markers as predictors of postoperative relapse showed that patients with any 1 positive predictor had a hazard ratio of about 27-fold to develop postoperative relapse (P = 0.001; 95% CI = 11.42–64.40). The interval between the detection of all 4 positive mRNA markers and subsequently developed postoperative relapse ranged from 4 to 10 months (median: 7 months). Furthermore, the expression of all 4 mRNA markers in all stage II CRC patients, or either stage II colon or rectal cancer patients were strongly correlated with poorer relapse-free survival rates by survival analyses (all P < 0.001).

Conclusions: The pilot study suggests that the constructed membrane-array method for the detection of CTCs is a potential auxiliary tool to conventional clinicopathological variables for the prediction of postoperative relapse in stage II CRC patients who have undergone curative resection.

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Colorectal cancer (CRC) is one of the most frequent malignancies and is also the third major cause of cancer-related death in Taiwan, with over 8000 new cases and 4000 deaths per year (http://www.doh.gov.tw/statistic/index.htm; accessed in January 2007). Adjuvant chemotherapy with 5-fluorouracil (FU)-based therapy has now become an accepted standard of care for patients with International Union Against Cancer (UICC) stage III colon cancer since the early 1990s, and has resulted in a 30% to 40% decrease in relapse and mortality rates versus treatment with surgery alone.1–3 More recently, the addition of oxaliplatin to 5-FU-based therapy has further improved patient outcomes, thus establishing this combination as a new standard of care.4,5 Patients with stage II CRC are generally considered to be at low risk for developing postoperative relapse; therefore, patients with CRC in this stage are not recommended to undergo routine
adjuvant chemotherapy. However, about 25% to 30% of CRC patients with stage II disease are at high risk for postoperative relapse. Indeed, the clinical outcome of patients with high-risk stage II disease is similar to that of patients with stage III disease.

With regard to stage II CRC, a wide variety of potential clinical and pathologic risk factors for recurrence have been investigated. The most important factors for predicting the risk of recurrence are emergency presentation (bowel perforation or obstruction), poorly differentiated tumor (histologic grade), depth of tumor invasion and adjacent organ involvement (T4), extramural venous invasion, and peritoneal involvement. Recently, we have also demonstrated that the depth of invasion, the presence of vascular invasion and number of examined lymph nodes may prominently affect the prognosis of patients with stage II CRC. It is therefore of high importance to define reliable prognostic factors for this patient group to help identify high-risk patients (for tumor relapse) who might benefit from adjuvant therapeutic regimes.

With recent developments in molecular technology, the use of polymerase chain reaction (PCR), reverse transcription-PCR (RT-PCR), or real-time quantitative-CR (Q-PCR) assays now permit sensitive detection of circulating tumor cells (CTCs) in peripheral blood. Accumulated reports have described the detection of CTCs in the peripheral blood of CRC patients, which has important prognostic and therapeutic implications. Our recently developed membrane array-based multimarker assay can detect CTCs in the peripheral blood of CRC patients; this is found to be a rational approach for the surveillance of postoperative CRC patients. Though many mRNA (messenger RNA) molecular markers have been evaluated as putative prognostic markers in CRC patients, no information about the multimarker assay [human telomerase reverse transcription (hTERT), cytokeratin-19 (CK-19), cytokeratin-20 (CK-20), and carcinoembryonic antigen (CEA)] in the detection of CTCs as a prognostic tool for stage II CRC patients has ever been obtained. The aim of this study was to analyze stage II CRC patients who have undergone curative resection by a panel of molecular markers using a constructed membrane-array method and evaluate their significance in postoperative surveillance.

**PATIENTS AND METHODS**

**Patients and Samples**

Included in this prospective study were 194 stage II CRC patients admitted to the Department of Surgery of Kaohsiung Medical University Hospital for elective surgery between January 2002 and December 2005. Patients with other malignant disease in their medical history were excluded. Circulating tumor cells in peripheral blood of these 194 patients were detected using our constructed membrane-array method. All 194 patients underwent radical resection for the primary lesion. Radical (R0) resection is defined as any gross residual tumor that did not remain in the surgical bed, and the surgical resection margin is pathologically negative for tumor invasion. Postoperative surveillance consisted of medical history, physical examination, and laboratory studies, including serum CEA levels every 3 months. Abdominal ultrasonography or computed tomography was performed every 6 months, and chest radiography and total colonoscopy were performed once a year. Patients were followed up at 3-monthly intervals for 2 years and 6-monthly intervals thereafter; median follow up was 40 months (range, 14–62 months). The development of new recurrent or metastatic lesions after operation was defined as a postoperative relapse. The type of postoperative relapse was designated as local recurrence (tumor growth restricted to the anastomosis or the region of primary operation) or distant metastases (distant metastases or diffuse peritoneal seeding). A 4-mL sample of peripheral blood was obtained from each CRC patient postoperatively (at least 1 week after surgery) for total RNA isolation. No additional blood samples were drawn for the detection of CTCs. To prevent contamination of epithelial cells, peripheral blood samples were obtained through a catheter inserted into a peripheral vessel, and the first 5 mL of blood were discarded. Written informed consent was obtained from each subject and/or guardian. Sample acquisition and subsequent use were also

| TABLE 1. Clinopathologic Characteristics of 194 Stage II Colorectal Cancer Patients |
|--------------------------------|----------------|----------------|
| **Variables**                | **No. (%)**   |
| Gender                       | 105 (54.1)/89 (45.9) |
| Age (yr)                     | 84 (43.3)/110 (56.7) |
| Maximum tumor size (cm)      | 100 (51.5)/94 (48.5) |
| Tumor location               | 128 (66)/66 (34) |
| Depth of tumor invasion      | 185 (95.4)/9 (4.6) |
| Vascular invasion            | 52 (26.8)/142 (73.2) |
| Perineural invasion          | 66 (34)/128 (66) |
| Histology                    | 17 (8.8)/157 (80.9)/20 (10.3) |
| Type of tumor                | 10 (5.2)/184 (94.8) |
| Mucinous carcinoma           | 53 (27.3)/141 (72.7) |
| Number of examined lymph nodes | 119 (61.3)/75 (38.7) |
| Preoperative colonic obstruction/perforation | 10 (5.2)/184 (94.8) |
| Adjuvant chemotherapy        | 125 (64.4)/69 (35.6) |

WD indicates well differentiated; MD, moderately differentiated; PD, poorly differentiated.
TABLE 2. Correlation Between Postoperative Relapse and Clinicopathologic Features of Stage II Colorectal Cancer Patients Using Univariate Analysis

<table>
<thead>
<tr>
<th></th>
<th>Postoperative Relapse (+) (N = 56) (%)</th>
<th>Postoperative Relapse (−) (N = 138) (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male/female</td>
<td>28 (50)/28 (50)</td>
<td>77 (55.8)/61 (44.2)</td>
<td>.463</td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65/≥65</td>
<td>20 (35.7)/36 (64.3)</td>
<td>64 (46.4)/74 (53.6)</td>
<td>.174</td>
</tr>
<tr>
<td>Maximum size (cm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5/≥5</td>
<td>27 (48.2)/29 (51.8)</td>
<td>73 (52.9)/65 (47.1)</td>
<td>.554</td>
</tr>
<tr>
<td>Tumor location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon/rectum</td>
<td>36 (64.3)/20 (35.7)</td>
<td>92 (66.7)/46 (33.3)</td>
<td>.751</td>
</tr>
<tr>
<td>Depth of tumor invasion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T&lt;sub&gt;1&lt;/sub&gt;/T&lt;sub&gt;4&lt;/sub&gt;</td>
<td>48 (85.7)/8 (14.3)</td>
<td>137 (99.3)/1 (0.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Vascular invasion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes/no</td>
<td>34 (60.7)/22 (39.3)</td>
<td>18 (13)/120 (87)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Perineural invasion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes/no</td>
<td>25 (44.6)/31 (55.4)</td>
<td>41 (29.7)/97 (70.3)</td>
<td>.048</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WD/MD/PD</td>
<td>3 (5.4)/44 (78.5)/9 (16.1)</td>
<td>14 (10.1)/113 (81.9)/11 (8)</td>
<td>.163</td>
</tr>
<tr>
<td>Mucinous carcinoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes/no</td>
<td>3 (5.4)/53 (94.6)</td>
<td>7 (5.1)/131 (94.9)</td>
<td>.935</td>
</tr>
<tr>
<td>Four molecular markers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes/no</td>
<td>45 (80.4)/11 (19.6)</td>
<td>8 (5.8)/130 (94.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Number of examined lymph nodes</td>
<td>41 (73.2)/15 (26.8)</td>
<td>78 (56.5)/60 (43.5)</td>
<td>.031</td>
</tr>
<tr>
<td>Preoperative colonic obstruction/perforation</td>
<td>3 (5.4)/53 (94.6)</td>
<td>7 (5.1)/131 (94.9)</td>
<td>.935</td>
</tr>
<tr>
<td>Adjuvant chemotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes/no</td>
<td>34 (60.7)/22 (39.3)</td>
<td>91 (65.9)/47 (34.1)</td>
<td>.491</td>
</tr>
</tbody>
</table>

WD indicates well differentiated; MD, moderately differentiated; PD, poorly differentiated.

approved by the hospital’s institutional review board. Clinical stage and pathologic features of primary tumors were defined according to the criteria of the American Joint Commission on Cancer/International Union Against Cancer (AJCC/UICC). Twenty-two patients were included in the study. The average age was 64.9 years (range, 28–90 years). With regard to the histologic type of tumors, 45.9% were well differentiated, 44.6% were moderately differentiated, and 9.5% were poorly differentiated.

mRNA Isolation and First Strand cDNA Synthesis

Total RNA was extracted from the fresh whole blood of CRC patients and healthy volunteers using a QIamp RNA Blood Mini Kit (QIAGEN Inc., Valencia, CA) according to the manufacturer’s instructions. The RNA concentration was determined spectrophotometrically on the basis of absorbance at 260 nm. First strand cDNA was synthesized from total RNA by using a RT-PCR kit (Promega Corp., Madison, WI).

Membrane-Arrays

The procedure of the membrane-array method for the detection of CTC-related mRNA molecular markers was performed according to our recent work. Patients overexpressing all 4 molecular markers by membrane-array methods were considered as positive results. In our previous investigation, the sensitivity limit of this technique was established at approximately 1 tumor cell per 10<sup>6</sup> white blood cells (5 cells per 1 mL blood).

Statistical Analysis

All data have been statistically analyzed using the Statistical Package for the Social Sciences, version 11.5 (SPSS Inc., Chicago, IL). A P value less than 0.05 was considered to be statistically significant. Two-sided Pearson χ<sup>2</sup> test and the Fisher exact test were used to analyze the potential correlation between the expression of molecular markers used in combination and the clinicopathologic features of the study subjects. The multivariate analysis of independent prognostic factors for postoperative relapse was determined using the logistic regression analysis. The relapse-free survival rates of CRC patients were further categorized according to the tumor location. The relapse-free survival rates were calculated by the Kaplan-Meier method, and the differences in survival rates were analyzed by the log-rank test.

RESULTS

One hundred five men (54.1%) and 89 women (45.9%) were included in the study. The average age was 64.9 years (range, 28–90 years). With regard to the histologic type of tumors, 45.9% were well differentiated, 44.6% were moderately differentiated, and 9.5% were poorly differentiated.
these tumors, 17 (8.8%) were well-differentiated, 157 (80.9%) were moderately well differentiated, and 20 (10.3%) were poorly differentiated carcinomas. The clinicopathologic characteristics of these 194 stage II patients are listed in Table 1. Overall, 53 of 194 (27.3%) patients were detected with the expression of all 4 mRNA markers using the membrane-array method. During the follow-up period, 36 of 128 (28%) colon cancer patients and 20 of 66 (30%) rectal cancer patients were identified with postoperative relapse. The sensitivity and specificity of the membrane-array method for the prediction of postoperative relapse was 80.4% (45 of 11) and 94.2% (130 of 138), respectively. Eight patients (15%) with positive result of molecular marker expression did not develop postoperative relapse, whereas 11 patients (7.8%) without positive result of molecular marker expression developed postoperative relapse subsequently.

From the correlation between postoperative relapse and clinicopathologic features or molecular markers of stage II CRC patients using univariate analyses, depth of tumor invasion ($P < 0.001$), vascular invasion ($P < 0.001$), perineural invasion ($P = 0.048$), positive molecular markers ($P < 0.001$), and the number of examined lymph nodes ($P = 0.031$) were statistically significant (Table 2). No significant differences existed between the positive molecular markers and the presence of local recurrence or distant metastasis respectively, in either colon or rectal cancer patients (both $P > 0.05$; Table 3).

Using a multivariate logistic regression analysis, the depth of invasion ($P = 0.013$; hazard ratio $= 4.080$), vascular invasion ($P = 0.032$; hazard ratio $= 3.541$), and positive molecular markers ($P < 0.001$; hazard ratio $= 38.597$) were demonstrated to be independent predictors for postoperative relapse (Table 4). Moreover, the combination of depth of tumor invasion, vascular invasion, and 4 positive molecular markers as high-risk predictors of postoperative relapse is shown in Table 5. Stage II CRC patients with 1 high-risk

### Table 3. Circulating Tumor Cells Used for the Prediction of Postoperative Relapse (Local Recurrence and Distant Metastasis) in 36 Colon and 20 Rectal Cancer Patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>Local Recurrence</th>
<th>Distant Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon (N = 28)</td>
<td>Rectum (N = 12)</td>
<td>Colon (N = 8)</td>
</tr>
<tr>
<td>Four molecular markers</td>
<td>Positive</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>2</td>
</tr>
</tbody>
</table>

### Table 4. Correlation Between Postoperative Relapse and Clinicopathologic Features of Stage II Colorectal Cancer Patients Using Multivariate Logistic Regression Analysis

<table>
<thead>
<tr>
<th>Variables</th>
<th>$\beta$</th>
<th>SE</th>
<th>$P$</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depth ($T_4/T_3$)</td>
<td>1.406</td>
<td>0.565</td>
<td>.013</td>
<td>4.080</td>
<td>2.348–11.348</td>
</tr>
<tr>
<td>Vascular invasion (yes/no)</td>
<td>2.684</td>
<td>0.911</td>
<td>.032</td>
<td>3.541</td>
<td>1.681–13.432</td>
</tr>
<tr>
<td>Four molecular markers (yes/no)</td>
<td>3.653</td>
<td>0.520</td>
<td>&lt;.001</td>
<td>38.597</td>
<td>13.931–106.938</td>
</tr>
</tbody>
</table>

$\beta$ indicates coefficient; SE, standard error; CI, confidence interval.

### Table 5. Combination of the Depth, Vascular Invasion, and Molecular Markers as Predictors of Postoperative Relapse for Stage II Colorectal Cancer Patients

<table>
<thead>
<tr>
<th>T4 or Vascular Invasion (+) or Molecular Markers (+)</th>
<th>No. Relapse Patients (n = 56)</th>
<th>No. Nonrelapse Patients (n = 138)</th>
<th>$P$</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any one predictor</td>
<td>48</td>
<td>25</td>
<td>&lt;.001</td>
<td>27.12</td>
<td>11.421–64.397</td>
</tr>
<tr>
<td>Positive</td>
<td>8</td>
<td>113</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

CI indicates confidence interval.
A predictor had a relative risk of 27.12 of developing postoperative relapse compared with those without any 1 high-risk predictor \((P < 0.001)\). The lead-time between the detection of all 4 positive molecular markers and subsequently developed postoperative relapse ranged from 4 to 10 months (Fig. 1; median: 7 months). Furthermore, statistically significant difference was observed in terms of relapse-free survival rate between CRC patients with expression of all 4 markers and those with less than 4 positive markers using the log-rank test, in all patients with CRC, and in colon cancer or rectal cancer (Fig. 2; all \(P < 0.001\)).

**DISCUSSION**

Patients who undergo radical resection of stage II primary CRC are reported to have a 5-year survival rate of around 75%.24 There is growing evidence that the prognosis of certain stage II CRC patients with unfavorable prognostic factors can be improved by adjuvant chemotherapy.25,26 Accordingly, there is clearly a need to identify novel predictive factors to guide the identification of stage II CRC patients who are likely to experience relapse. More recently, there has been an attempt to identify novel panels of molecular and biochemical markers that may be used to more precisely define prognosis, and predict benefit of adjuvant treatment in CRC. Several retrospective studies have suggested that a number of molecular markers may now define patients with a higher risk of relapse with both stage II and stage III disease.27–30 However, none of these are currently in clinical application regarding the decision whether patients with stage II CRC should receive adjuvant chemotherapy.

Detection of micrometastases and CTCs in patients with malignancies undergoing surgery for cure remains a challenge for oncologists, because dissemination of neoplastic cells is the main determinant of distant relapse and cancer-related death. There are numerous publications about conventional RT-PCR or Q-PCR detection of CTCs in CRC patients,14 –17,31,32 but 1 of the limitations is that the methodology could analyze only 1 molecular target at a time. Because of the heterogeneity of tumor-related genes, a multimarker assay is regarded as more reliable and sensitive than a single marker assay.33–35 Our membrane-array assay was able to simultaneously detect a panel of informative molecular markers for the presence of CTCs in stage II CRC patients, with advantages of time-saving and cost-effectiveness.18 Consistent with our findings, Koch e al also showed the prognostic significance of tumor cells detected in blood samples of patients with stage II CRC using CK-20 RT-PCR.36 Similarly, Lloyd et al have disclosed that for a subgroup of patients with stage I and II CRC, detection of twenty-eight stage II colon cancer patients with all 4 mRNA markers expression in the peripheral blood showed a significantly poorer survival rate than those with less than 4 positive mRNA marker expression \((P < 0.001)\); C, Sixty-six stage II rectal cancer patients with all 4 mRNA markers expression in the peripheral blood showed a significantly poorer survival rate than those with less than 4 positive mRNA marker expression \((P < 0.001)\).
marker-positive cells by immunobead RT-PCR in peritoneal lavage fluid taken during laparotomy was a significant risk factor for reduced survival after curative resection. This risk factor was independent of the established prognostic factors of tumor stage and site of primary tumor and may be useful in determining those patients who would benefit from adjuvant chemotherapy.

Conversely, some recently published studies report conflicting results regarding the prognostic value of CTCs. A major problem of most of the published studies is that only small, inhomogeneous patient groups with short follow-up periods were evaluated. Moreover, the methods used for CTCs detection also need to be taken into account, as sensitivity and specificity are of major importance and may differ significantly. A false positive rate of 15% and a false negative rate of 7.8% for the prediction of postoperative relapse using our membrane-array assay suggest that there is room for the improvement of this method. In fact, using microarray technology and gene-expression profiling to identify more specific markers of risk of relapse in stage II patients might improve the accuracy of molecular detection methods.

Despite curative resection, 28.9% of Stage II CRC patients ultimately developed postoperative relapse in our observation. Our constructed membrane-array method could detect CTCs in 80% of these stage II CRC patients with postoperative relapse. This method is helpful for the prediction of both local recurrence and distant metastasis in either colon or rectal cancer patients postoperatively. Multivariate analysis revealed 3 independent prognostic markers in our patient cohort, including T4 depth of tumor invasion, the presence of vascular invasion and all 4 molecular markers. Likewise, Koch et al confirmed that tumor cell detection in blood, T-category and number of removed lymph nodes to be independent prognostic factors for survival rates of stage II CRC patients. Overall, stage II CRC patients with 1 high-risk predictor, T4 or positive vascular invasion or all 4 molecular markers, have a 27-fold risk of developing postoperative relapse compared with those without any 1 high-risk predictor. Concomitant molecular diagnosis of CTCs with a biomarker panel is a justifiable supplementary approach to the current pathologic staging system, which may help physicians make appropriate judgments on clinical management and predictive prognosis for stage II CRC patients. Hence, therapeutic decision-making models are likely to be further redefined by the inclusion of such molecular markers.

Finally, this current investigation has demonstrated that our membrane-array methods could identify stage II CRC patients at high risk of relapse at an earlier stage, with a median lead-time (the time between the presence of molecular markers and the onset of clinically detectable recurrence) of 7 months. In practice, 7 months is adequate for the consideration of new therapeutic strategies to possibly cure these patients. Incidentally, the lead-time advantage of routine serum CEA measurement for surveillance of CRC patients is only 4 months. Therefore, it is an approximate 3-month benefit for the earlier prediction of postoperative relapse when comparing our membrane-array method and serum CEA measurement. Moreover, relapse-free survival rates of stage II colon or rectal cancer patients during a median follow up of 40 months are significantly lower in those patients with 4 molecular markers. Consequently, to determine whether the introduction of adjuvant chemotherapy for stage II patients with positive CTCs is advantageous and efficacious would be an imperative issue for future investigation.

In conclusion, the constructed membrane-array method for the detection of CTCs has been demonstrated to be complementary to the surveillance of stage II CRC patients. The highly sensitive and high-throughput assay is a promising tool for early detection of postoperative relapse, with a median lead-time of 7 months before the development of postoperative relapse. However, large scale and long-term clinical studies follow up is warranted, to confirm the clinical significance of membrane-arrays as decision-making models for adjuvant chemotherapy.

ACKNOWLEDGMENTS
The authors thank Drs. Wing-Yiu Lui, Chien-Yu Lu, and Jan-Sing Hsieh for having contributed financially and materially to the study.

REFERENCES


Inflammation-Based Prognostic Score Is a Novel Predictor of Postoperative Outcome in Patients With Colorectal Cancer

Mitsuru Ishizuka, MD, Hitoshi Nagata, MD, Kazutoshi Takagi, MD, Toru Horie, MD, and Keiichi Kubota, MD

Objective: To investigate the significance of preoperative Glasgow prognostic score (GPS) for postoperative prognostication of patients with colorectal cancer.

Background: Recent studies have revealed that the GPS, an inflammation-based prognostic score that includes only C-reactive protein (CRP) and albumin, is a useful tool for predicting postoperative outcome in cancer patients. However, few studies have investigated the GPS in the field of colorectal surgery.

Methods: The GPS was calculated on the basis of admission data as follows: patients with an elevated level of both CRP (>10 mg/L) and hypoalbuminemia (Alb <35 g/L) were allocated a score of 2, and patients showing 1 or none of these blood chemistry abnormalities were allocated a score of 1 or 0, respectively. Prognostic significance was analyzed by univariate and multivariate analyses.

Results: A total of 315 patients were evaluated. Kaplan-Meier analysis and log-rank test revealed that a higher GPS predicted a higher risk of postoperative mortality (P < 0.01). Univariate analyses revealed that postoperative TNM was the most sensitive predictor of postoperative mortality (odds ratio, 0.148; 95% confidence interval, 0.072–0.304; P < 0.0001). Multivariate analyses using factors such as age, sex, tumor site, serum carcinoembryonic antigen, CA19-9, CA72-4, CRP, albumin, and GPS revealed that GPS (odds ratio, 0.165; 95% confidence interval, 0.037–0.732; P = 0.0177) was associated with postoperative mortality.

Conclusions: Preoperative GPS is considered to be a useful predictor of postoperative mortality in patients with colorectal cancer.

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PATIENTS AND METHODS

We retrospectively reviewed a database of 315 patients (male:female = 186:129) who had undergone elective surgery for CRC performed by the same trained surgical team at the Department of Gastroenterological Surgery, Dokkyo University Hospital, between January 2001 and March 2006. Patients who had no laboratory data for CRP and albumin on the day of admission or who died immediately after surgery (within 30 days) and who died because of noncancer-related causes were excluded from the study.

Routine laboratory measurements including serum CRP, albumin, and tumor markers such as carcinoembryonic antigen (CEA) (cutoff value, 6 ng/mL), CA19-9 (cutoff value, 30 U/mL), and CA72-4 (cutoff value, 10 U/mL) were carried out on the same day to exclude any inflammatory effect of preoperative
sequential examinations, such as colonoscopy or barium enema. At this time, no patient showed clinical evidence of infection or any other inflammatory conditions, such as obstructive colitis. Moreover, no patient had received preoperative chemotherapy or irradiation.

The GPS was estimated as described previously. Briefly, patients with both elevated CRP (>10 mg/L) and hypoalbuminemia (<35 g/L) levels were allocated a score of 2. Patients with only one of these biochemical abnormalities were allocated a score of 1. Patients with neither of these abnormalities were allocated a score of 0.

Statistical Analysis

Data are presented as mean and range [95% confidence interval (CI)]. A CRP concentration exceeding 10 mg/L was considered to indicate the presence of a SIR, based on the findings from previous investigations. Differences between groups were analyzed using the Mann-Whitney U test and χ² test, and odds ratios (OR) with 95% CI were calculated using univariate or multivariate logistic regression analysis. Survival analysis was performed using the Cox proportional hazard model with patient age, sex, tumor site, CEA, CA19-9, CA72-4, CRP, albumin, Dukes staging, postoperative TNM classification, and GPS as prognostic variables. Kaplan-Meier analysis and log-rank test were used to compare mortality for each GPS. Deaths before May 31, 2006 were included in this analysis. Statistical analyses were performed using StatView software, version 5.0 (Abacus Concepts Inc., Berkley, CA) at a significance level of P < 0.05.

RESULTS

The classified background characteristics of the 315 patients who underwent surgery for CRC are shown in Table 1. There were 186 men and 129 women, 207 colon cancers and 108 rectal cancers. There were no significant differences in overall survival in terms of age (<70/≥70 years), sex (male/female), or tumor site (colon/rectum). On the other hand, significant differences in overall survival were observed in relation to CEA, CRP, albumin, Dukes staging, TNM classification, and GPS.

Table 2 shows the relationship between clinicolaboratory characteristics and GPS in patients with CRC. Age and sex showed no significant relationship with GPS classification. On the other hand, tumor site, tumor markers (CEA, CA19-9, and CA72-4), CRP, albumin, Dukes staging, and TNM classification each showed a close relationship with GPS classification. GPS2 (high GPS) patients not only had a higher proportion of rectal cancer than patients with GPS0 (low GPS) and GPS1 (medium GPS), but also had higher serum levels of tumor markers and CRP, and higher Dukes and TNM staging. GPS was not affected by age or sex. During the term of observation, 66 patients died of CRC.

There were 76 patients with a high level of CRP (≥10 mg/L). Forty-four of the 76 patients (57.9%) had hypoalbuminemia (<35 g/L).

Results of univariate analysis of postoperative mortality, using the same factors as those in Table 1, are presented in Table 3. All factors were associated with mortality except for age, sex, tumor site, and albumin. Postoperative TNM classification was the most sensitive predictors of postoperative mortality (OR, 0.148; 95% CI, 0.072–0.304; P < 0.0001).

Multivariate analyses using the same factors as those in Table 3 except for TNM classification revealed that GPS (OR, 0.165; 95% CI, 0.037–0.732; P = 0.0177) was associated with postoperative mortality (Table 4).

The median and minimum follow-up terms for survivors were 13.7 months and 11 days, respectively. Overall mean survival was 17.7 months (95% CI, 16.1–19.4), and log-rank test revealed that patients with a high GPS had a higher mortality rate than those with a low or medium (P < 0.01).

Kaplan-Meier analysis demonstrated significant differences among the 3 groups: GPS2 (mean survival, 13.7 months; 95% CI, 9.2–18.1 months), GPS1 (mean survival, 13.0 months; 95% CI, 10.5–15.5 months), and GPS0 (mean survival, 21.0 months; 95% CI, 18.7–23.3 months).

| TABLE 1. Classified Clinical and Laboratory Characteristics Associated with Overall Survival |
|--------------------------------------|-----------------|-----------------|-----------|
| Age (yr)  | No. Patients | Overall Survival (mo) | P* |
| <70       | 162          | 16.3 (13.8–18.7)    |
| ≥70       | 153          | 17.3 (14.8–19.8)    |
| Sex       |               |                   |         |
| Male      | 186          | 17.8 (15.5–20.0)    |
| Female    | 129          | 17.7 (15.2–20.2)    |
| Tumor site|               |                   |         |
| Colon     | 207          | 17.4 (15.3–19.4)    |
| Rectum    | 108          | 18.4 (15.6–21.3)    |
| CEA       |               |                   |         |
| <6 ng/mL  | 185          | 19.6 (17.4–21.8)    |
| ≥6 ng/mL  | 120          | 14.9 (12.3–17.4)    |
| CA19-9    |               |                   |         |
| <30 U/mL  | 185          | 19.1 (16.9–21.3)    |
| ≥30 U/mL  | 113          | 15.7 (13.1–18.2)    |
| CA72-4    |               |                   |         |
| <10 U/mL  | 192          | 17.3 (15.2–19.4)    |
| ≥10 U/mL  | 29           | 12.5 (8.0–17.0)     |
| C-reactive protein |   |                   |         |
| <10 mg/L  | 239          | 19.0 (17.1–21.0)    |
| ≥10 mg/L  | 76           | 13.6 (10.5–16.8)    |
| Albumin concentration |   |                   |         |
| <35 g/L   | 100          | 13.0 (10.5–15.6)    |
| ≥35 g/L   | 215          | 19.9 (17.9–22.0)    |
| Dukes staging |     |                   |         |
| A, B, C   | 233          | 19.4 (17.4–21.4)    |
| D         | 82           | 13.0 (10.5–15.5)    |
| TNM classification |   |                   |         |
| 0, 1, 2   | 146          | 19.6 (17.0–22.1)    |
| 3, 4      | 169          | 16.2 (14.0–18.3)    |
| GPS       |               |                   |         |
| 0         | 183          | 21.0 (18.7–23.3)    |
| 1         | 89           | 13.0 (10.5–15.5)    |
| 2         | 43           | 13.7 (9.2–18.1)     |

*Mann-Whitney U test.
Thus, the use of the GPS classification was able to clearly divide patients with CRC into 3 independent groups (Fig. 1).

### TABLE 2. Relationships Between Clinicoloratory Characteristics and GPS

<table>
<thead>
<tr>
<th></th>
<th>GPS0 (n = 183)</th>
<th>GPS1 (n = 89)</th>
<th>GPS2 (n = 43)</th>
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<tbody>
<tr>
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<td>(\geq70)</td>
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<td>21</td>
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<tr>
<td>Female</td>
<td>68</td>
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<td>Rectum</td>
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<td>(\geq6) ng/mL</td>
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<td>(\geq30) U/mL</td>
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<td>(\geq10) U/mL</td>
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<td>C-reactive protein</td>
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<td>&lt;10 mg/L</td>
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<td>56</td>
<td>0</td>
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<tr>
<td>(\geq10) mg/L</td>
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<td>43</td>
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<td>Albumin</td>
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<td>&lt;35 g/L</td>
<td>0</td>
<td>57</td>
<td>43</td>
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<td>(\geq35) g/L</td>
<td>183</td>
<td>32</td>
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<td>Dukes staging</td>
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<tr>
<td>A, B, C</td>
<td>153</td>
<td>56</td>
<td>24</td>
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<td>D</td>
<td>30</td>
<td>33</td>
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<td>3, 4</td>
<td>86</td>
<td>54</td>
<td>29</td>
<td>0.0156</td>
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</table>

*\( \chi^2 \) test

### TABLE 3. Univariate Logistic Regression Analysis in Relation to Mortality

<table>
<thead>
<tr>
<th></th>
<th>( P )</th>
<th>Odds Ratio</th>
<th>95% CI</th>
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<tr>
<td>Age (yr)</td>
<td>0.7814</td>
<td>0.996</td>
<td>0.972–1.022</td>
</tr>
<tr>
<td>Sex</td>
<td>0.2645</td>
<td>0.733</td>
<td>0.424–1.265</td>
</tr>
<tr>
<td>Tumor site</td>
<td>0.6892</td>
<td>1.122</td>
<td>0.637–1.977</td>
</tr>
<tr>
<td>CEA</td>
<td>0.0038</td>
<td>1.002</td>
<td>1.001–1.003</td>
</tr>
<tr>
<td>CA19-9</td>
<td>0.0040</td>
<td>1.001</td>
<td>1.000–1.001</td>
</tr>
<tr>
<td>CA72-4</td>
<td>0.0250</td>
<td>1.014</td>
<td>1.002–1.026</td>
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<tr>
<td>C-reactive protein</td>
<td>0.0156</td>
<td>1.143</td>
<td>1.026–1.275</td>
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<tr>
<td>Albumin</td>
<td>0.4883</td>
<td>0.851</td>
<td>0.539–1.343</td>
</tr>
<tr>
<td>Dukes (A, B, C/D)</td>
<td>(&lt;0.0001)</td>
<td>0.999</td>
<td>0.504–0.183</td>
</tr>
<tr>
<td>TNM (0, 1, 2 and 3, 4)</td>
<td>(&lt;0.0001)</td>
<td>0.148</td>
<td>0.072–0.304</td>
</tr>
<tr>
<td>GPS (0, 1 and 2)</td>
<td>0.0018</td>
<td>0.336</td>
<td>0.169–0.667</td>
</tr>
</tbody>
</table>

### TABLE 4. Multivariate Logistic Regression Analysis in Relation to Mortality

<table>
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<tr>
<th></th>
<th>( P )</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>0.7726</td>
<td>1.005</td>
<td>0.971–1.041</td>
</tr>
<tr>
<td>Sex</td>
<td>0.0827</td>
<td>0.519</td>
<td>0.247–1.089</td>
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<tr>
<td>Tumor site</td>
<td>0.7032</td>
<td>1.116</td>
<td>0.529–2.567</td>
</tr>
<tr>
<td>CEA</td>
<td>0.1558</td>
<td>1.003</td>
<td>0.999–1.006</td>
</tr>
<tr>
<td>CA19-9</td>
<td>0.1854</td>
<td>1.001</td>
<td>1.000–1.001</td>
</tr>
<tr>
<td>CA72-4</td>
<td>0.2638</td>
<td>1.009</td>
<td>0.993–1.026</td>
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<td>C-reactive protein</td>
<td>0.3907</td>
<td>0.891</td>
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<tr>
<td>Albumin</td>
<td>0.0821</td>
<td>1.984</td>
<td>0.916–4.297</td>
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<tr>
<td>GPS (0, 1 and 2)</td>
<td>0.0177</td>
<td>0.165</td>
<td>0.037–0.732</td>
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</table>

### DISCUSSION

This retrospective analysis based on individual data for 315 patients who had undergone surgery for CRC demonstrated that the GPS has prognostic value. Although the prognostic significance of the GPS has previously been reported for several kinds of cancer, those studies investigated only advanced cases, such as those that were inoperable or associated with metastasis.\(^2,5,7,9\) In contrast, the present study evaluated patients who underwent elective surgery for CRC, including not only inoperable cases, but also those with metastasis. To our knowledge, this study is the first to evaluate the use of GPS in patients undergoing colorectal surgery for CRC in a university teaching hospital, and the first to compare GPS with tumor markers in terms of prognostic value. In fact, it was noteworthy that univariate and multivariate analyses showed similar prognostic values for GPS and postoperative TNM classification. Although postoperative TNM is considered the current gold standard for predicting outcome by univariate analysis, surprisingly, multivariate analysis revealed that GPS was superior in this respect to CEA, CA19-9, or CA72-4.

Recently, a similar report by McMillan et al\(^10\) clearly demonstrated that the “modified GPS” was significantly associated with overall and cancer-specific survival in Dukes B CRC. However, our data revealed that GPS was a useful predictor of postoperative mortality in patients of all Dukes staging CRC.
Kaplan-Meier analysis of the patients as a whole showed that they were clearly divisible into 3 independent groups on the basis of GPS classification, and that a higher GPS was associated with a poorer outcome of colorectal surgery. It is well known that the Dukes classification is a good prognostic indicator for patients with CRC because it includes pathologic findings that are revealed postoperatively. In contrast, the GPS is able to clearly classify patients with CRC into 3 independent groups on the basis of preoperative laboratory data only. Recent innovative forms of systemic chemotherapy such as the FOLFIRI (FOL: folinic acid [leucovorin], F: fluorouracil [5-Fu], IRI: irinotecan [Camptosar]) and FOLFOX (FOL: folic acid [leucovorin], F: fluorouracil [5-Fu], OX: oxaliplatin [Eloxatin]) regimens have helped to reduce postoperative mortality. As a result, the survival rate of Dukes C patients has now approached that of Dukes B patients. However, our present results revealed that the GPS is not affected by factors such as pathologic findings and postoperative chemotherapy because it includes only serum CRP and albumin, which are affected by SIR.

In general, conventional tumor markers such as CEA, CA19-9, and CA72-4 are well known to be significant indicators of tumor growth or recurrence, as they are thought to be secreted from the tumor itself. On the other hand, use of the GPS for prediction of postoperative outcome reflects different factors. First, as the GPS is calculated simply from the serum levels of CRP and albumin, it is thought to reflect SIR in the tumor microenvironment. CRP is an acute-phase protein produced by the liver, and is elevated in response to inflammation and cancer. These reports suggest a close relationship between inflammation and cancer.

The mechanism of CRP upregulation is controlled by cytokines, such as interleukin-8 (IL-8), interleukin-6 (IL-6), and tumor necrosis factor α. Thus, high CRP levels might reflect an increased level of IL-6 in patients with advanced cancer. However, in most cases, evaluation of interleukins is not performed routinely in hospitals at the time of admission, so instead CRP can be considered an indirect indicator of upregulation of interleukins, particularly IL-6. Increased CRP levels in patients with cancer could also be caused by an inflammatory response to tumor infiltration or the microenvironment of a tumor infiltrated by lymphocytes, reflecting immunoreactive processes. Indeed, there is increasing evidence that a high level of serum CRP is also correlated with shorter survival in patients with gastrointestinal malignancies, including cancers of the esophagus, stomach, biliary system, and colorectum.

Second, recent reports have also revealed that serum albumin is related to the SIR. In this regard, the presence of a SIR, as reflected by the GPS, may lead to malnutrition and functional deterioration, ultimately resulting in increased mortality. In particular, recent studies have revealed that albumin concentration is a stage-independent prognostic factor in patients with advanced CRC. Indeed, this concept is consistent with the fact that all patients with hypoalbuminemia have an elevated CRP concentration.

Third, with regard to the prognostication of patients using GPS, the present results underline that the SIR bulk estimation is well accepted as an indicator of tumor growth, and that using 2 familiar parameters (CRP and albumin) is efficient to predict postoperative outcome. Though GPS distribution showed significant differences among patients with different Dukes stages (data not shown), GPS may be a useful tool for deciding the operability of patients at each Dukes stage or whether postoperative chemotherapy is indicated. Although GPS alone cannot be used to decide operability or use of chemotherapy, it may be helpful in cases in which such issues are unclear. For example, although it is still controversial whether synchronous or metachronous hepatectomy should be done for Dukes D cases (in which there are multiple liver metastases), synchronous hepatectomy may be more actively acceptable for such cases in which the GPS is 0 than for those in which it is 1 or 2. On the other hand, early postoperative chemotherapy may be more positively acceptable for Dukes C cases in which the GPS is 2 than for those in which it is 0 or 1.

Finally, recent studies have revealed that CRP is a useful indicator of metachronous liver metastasis. Therefore, GPS should be routinely evaluated in blood chemistry examinations for outpatient because of its lower cost and greater convenience in comparison with complex and expensive techniques such as computed tomography, magnetic resonance imaging, and positron emission tomography. Postoperative CRC outpatients showing an increased GPS may be scrutinized more closely for recurrence, because of their higher risk. Thus, it may be possible to improve the overall survival of patients with CRC after treatment by determining the GPS routinely at the time of admission or on an outpatient basis.

In conclusion, worldwide adoption of the GPS as a simple and convenient tool for postoperative prognostication of patients with CRC may be considerably beneficial.

REFERENCES


Objective: To clarify the optimal surgical strategy for Bismuth type I and II hilar cholangiocarcinomas.

Summary Background Data: Local or hilar resections is often performed for Bismuth type I and II tumors; however, reported outcomes have been unsatisfactory with a high recurrence and low survival rate. To improve survival, some authors have recommended right hepatectomy. However, the clinical value of this approach has not been validated.

Methods: Records of 54 consecutive patients who underwent resection of a Bismuth type I or II hilar cholangiocarcinoma were analyzed retrospectively. Through 1996, bile duct resection or the smallest necessary hepatic segmentectomies was performed. Beginning in 1997, choice of resection was based on the cholangiographic tumor type. For nodular or infiltrating tumor, right hepatectomy was indicated; for papillary tumor, bile duct resection with or without limited hepatectomy was chosen.

Results: Right hepatectomy was performed in 5 (20.8%) of 24 patients through 1996 and was done in 22 (73.3%) of 30 patients from 1997 (P = 0.0003). In patients without pM1 disease, R0 resection was achieved more frequently in the later period than in the earlier period (23 of 24 = 95.8% vs. 13 of 21 = 61.9%, P = 0.0073), which lead to better survival (5-year survival, 44.3% vs. 25.0%, P = 0.0495). In the 31 patients with nodular or infiltrating tumor, who tolerated surgery and did not have pM1 disease, survival was better in the 18 patients who underwent right hepatectomy than in those who did not (5-year survival, 62.9% vs. 23.1%, P = 0.0030). In cases of papillary tumor, bile duct resection with or without limited hepatectomy was sufficient to improve long-term survival.

Conclusions: The surgical approach to Bismuth type I and II hilar cholangiocarcinomas should be determined according to cholangiographic tumor type. For nodular and infiltrating tumors, right hepatectomy is essential; for papillary tumor, bile duct resection with or without limited hepatectomy is adequate.


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Surgical Approach to Bismuth Type I and II Hilar Cholangiocarcinomas

Audit of 54 Consecutive Cases

Takashi Ikeyama, MD, Masato Nagino, MD, Koji Oda, MD, Tomoki Ebata, MD, Hideki Nishio, MD, and Yuji Nimura, MD

Recently, with improvement of diagnostic and surgical techniques, many surgeons have adopted an aggressive approach to hilar cholangiocarcinoma with satisfactory results.1–10 Liver resection is now commonly performed for this difficult disease, and combined en bloc resection of the caudate lobe has become standard practice. Moreover, portal vein resection1,2,11–13 and/or hepatopancreatoduodenectomy14,15 have been performed in selected patients with advanced disease. However, several questions remain unsolved. One controversy exists regarding the procedure of choice for patients with Bismuth type I or II tumors.16,17 Several authors13,4,7 have reported that, in principle, patients with Bismuth type I or II tumors can undergo local or hilar resections including the extrahepatic suprapancreatic biliary tract. Other authors18 have recommended left hepatectomy, as this resection is the most versatile procedure for hilar cholangiocarcinoma, affording high resectability, safety, and good quality of postoperative life. Others5,6,10 recommend right hepatectomy because the right hepatic artery passes behind the proximal portion of the common hepatic duct and, therefore, is often invaded by cancer. Performance of right hepatectomy, in theory, seems to be rational; however, its survival impact has not been validated clinically. The aim of the present study was to establish the best surgical strategy for Bismuth type I and II hilar cholangiocarcinomas.

MATERIALS AND METHODS

Patients

From January 1979 to December 2005, 351 patients with hilar cholangiocarcinoma underwent resection at The First Department of Surgery, Nagoya University Hospital. The procedures included 17 (4.8%) bile duct resections and 334 (95.2%) hepatectomies with or without portal vein resection and/or pancreatoduodenectomy.11–15 According to the Bismuth classification criteria, type I, II, III, and IV tumors were found in 24 (6.8%), 30 (8.5%), 148 (42.2%), and 149 (42.5%) patients, respectively. In this study, we reviewed data from the 54 patients with Bismuth type I or II tumor (31 men and 23 women, mean age of 61.4 ± 10.1 year).

Forty-six (85.2%) were jaundiced on admission, with a mean total serum bilirubin concentration of 10.0 ± 5.7 mg/dL (range, 3.0–24.5 mg/dL). Percutaneous transhepatic biliary
drainage was performed in 53 patients, including 7 nonjaundiced patients who had intrahepatic biliary dilatation, to relieve obstruction or to determine the extent of disease along the individual intrahepatic segmental ducts.

Preoperative right portal vein embolization was carried out in 21 (77.8%) of 27 patients who underwent right hepatectomy. This radiologic intervention was performed via the percutaneous transhepatic approach approximately 2 weeks before hepatectomy.19,20

**Surgical Strategy**

We changed our surgical strategy for Bismuth type I and II hilar cholangiocarcinoma after 1996. In an early period (from 1979 through 1996), we chose, in principle, less extensive procedures such as bile duct resection or the smallest hepatic segmentectomy necessary to obtain clear surgical margins.21 Right hepatectomy was indicated only in patients in whom involvement of the right hepatic artery carried a high index of suspicion or in patients with superficial cancer spreading to the right-sided intrahepatic bile ducts. In a late period (from 1997 through 2005), the type of resection was based on the gross appearance of the tumor on cholangiogram, papillary, nodular, or infiltrating (Fig. 1). Right hepatectomy was indicated in patients with nodular or infiltrating tumors unless they had pM1 disease or poor hepatic function. In patients with papillary tumor, bile duct resection or limited hepatectomy was chosen according to the extent of cancer extension. Through the entire study period, portal vein resection11,12 and/or pancreatoduodenectomy15 were aggressively performed whenever necessary for curative resection.

**Histologic Evaluation**

The surgical specimens were fixed in 10% formalin for several days, and serially sectioned at 5-mm intervals. The specimens were prepared in the usual manner for microscopic examination using hematoxylin and eosin stains. Pathologic findings were described using the TNM Classification of Malignant Tumors by the International Union Against Cancer (6th edition, 2002).22

Involvement of the resected right hepatic artery was histologically assessed in 20 patients with nodular or infiltrating tumor, who underwent right hepatectomy with caudate lobectomy in the late period. Microscopic invasion of the artery was classified as grade 0 (no involvement), grade I (invasion limited to the tunica adventitia), or grade II (cancer invasion reaching the tunica media or intima). In patients with grade 0 invasion, the distance between the leading edge of the cancer and the outer layer of the tunica adventitia was measured.

**Statistics**

Results are expressed as the mean ± standard deviation. Statistical analysis was performed using Student t test, χ² test, and Fisher exact test probability test, where appropriate. Postoperative survival was calculated using the Kaplan-Meier method. Differences in survival curves were compared using the log rank test. P < 0.05 was considered statistically significant.

**RESULTS**

**Surgical Procedures Performed**

In the early period, 24 patients underwent resection (Table 1, Fig. 2). Of them, 19 patients underwent bile duct resection (n = 11) or limited hepatectomy less than right hepatectomy (n = 8). Right hepatectomy with caudate lobectomy was performed only in 5 patients: 4 patients in whom involvement of the right hepatic artery was suspected; and 1 patient with superficial cancer spreading to the right-sided intrahepatic bile ducts.

<table>
<thead>
<tr>
<th>TABLE 1. Demographics and Surgical Procedures</th>
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</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td>1979–1996 (n = 24)</td>
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<tr>
<td>1997–2005 (n = 30)</td>
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<tr>
<td></td>
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<tr>
<td>Age (yr)</td>
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<tr>
<td>59.5 ± 10.5</td>
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<td>62.9 ± 9.8</td>
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<td>Gender (male/female)</td>
</tr>
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<td>15/9</td>
</tr>
<tr>
<td>16/14</td>
</tr>
<tr>
<td>0.50</td>
</tr>
<tr>
<td>Obstructive jaundice on admission</td>
</tr>
<tr>
<td>21 (87.5)</td>
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<tr>
<td>25 (83.3)</td>
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<td>0.72</td>
</tr>
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<td>Surgery</td>
</tr>
<tr>
<td>Type of hepatectomy</td>
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<tr>
<td>Right hepatectomy + S1</td>
</tr>
<tr>
<td>5 (20.8)</td>
</tr>
<tr>
<td>22 (72.5)</td>
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<tr>
<td>Others</td>
</tr>
<tr>
<td>19 (79.2)</td>
</tr>
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<td>8 (26.7)</td>
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<td>Left hepatectomy + S1</td>
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<td>S4 + S1</td>
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<td>2</td>
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<tr>
<td>11</td>
</tr>
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<td>3</td>
</tr>
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<td>Combined resection</td>
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<td>Portal vein</td>
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<td>6 (25.0)</td>
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<td>7 (23.3)</td>
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<td>Pancreatoduodenectomy</td>
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<td>9 (30.0)</td>
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<td>Curability</td>
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<td>R0 resection</td>
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<td>25 (83.3)</td>
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<td>0.12</td>
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<td>R1 resection</td>
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<td>5* (16.7)</td>
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<td>R2 resection</td>
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<td>2* (8.3)</td>
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<tr>
<td>Mortality</td>
</tr>
<tr>
<td>2 (8.3)</td>
</tr>
<tr>
<td>1 (3.3)</td>
</tr>
<tr>
<td>0.58</td>
</tr>
</tbody>
</table>

Values inside parentheses indicate percentages.
S1, S4, and S5 indicates resection of each segment.
*All patients had nodular or infiltrating tumor.

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In the late period, 30 patients underwent resection (Table 1, Fig. 2). Among the 24 patients with nodular or infiltrating tumor, 20 patients underwent right hepatectomy with caudate lobectomy, and the remaining 4 patients underwent bile duct resection (n/H11005 1) or limited hepatectomy less than right hepatectomy (n/H11005 3), due to para-aortic lymph node metastasis (n/H11005 2), liver metastasis (n/H11005 1), or poor liver function (n/H11005 1). Among the 6 patients with papillary tumor, 2 patients underwent bile duct resection, and 2 other patients underwent isolated caudate lobectomy. The remaining 2 patients underwent right hepatectomy with caudate lobectomy due to superficial cancer spreading to the right-sided intrahepatic bile ducts.

Right hepatectomy with caudate lobectomy was performed in 5 (20.8%) of the 24 patients in the early period and was done in 22 (73.3%) of the 30 patients in the late period (P = 0.0003). Portal vein resection was indicated in patients with invasion of the portal vein, and pancreatoduodenectomy was performed in patients with extensive distal extension of the cancer. These combined resections were evenly divided between the 2 periods. The frequency of R0 resection was achieved frequently in the late period compared with the early period (83.3% vs. 62.5%), although the difference was not statistically significant (Table 1).

Three patients died of postoperative complications, yielding a mortality rate of 5.6%. In the early period, 1 patient who underwent hilar bile duct resection with pancreatoduodenectomy died of intraabdominal bleeding on postoperative day (POD) 51. Another patient who underwent right hepatectomy with pancreatoduodenectomy and portal vein resection died of multiple organ failure on POD 16. In the late period, 1 patient who underwent right hepatectomy with pancreatoduodenectomy and portal vein resection died of liver failure on POD 15 (Table 1).

### Macroscopic and Microscopic Findings of Tumor

Macroscopic and microscopic pathology in the 2 study periods are compared in Table 2. There were no intergroup differences. Nodular or nodular infiltrating tumors were the most common type (n = 31, 57.4%), followed by papillary tumor (n = 13, 24.1%) then infiltrating tumor (n = 10, 18.5%). As to the relationship between surgical resectability and macroscopic tumor type, all R1 and R2 resections (n = 14) were of nodular or infiltrating tumors; in other words, all resections for papillary tumor resulted in R0 resection.

Nine patients (3 through 1996 and 6 from 1997) had pM1 disease, including para-aortic lymph node metastasis (n = 5), local dissemination (n = 3), and small liver metastasis (n = 1). The percentage of R0 resection was not significantly different in the 2 study periods as mentioned above (Table 1). However, focusing on patients with pM0 disease, the percentage of R0 resection was higher in the late period (75.0% vs. 66.7%).
period than in the early period (23 of 24 = 95.8% vs. 13 of 21 = 61.9%, \( P = 0.0073 \)).

**Survival According to the Study Periods**

The 3- and 5-year survival rates (including all deaths) were 29.2% and 25.0% in the early period, and 62.8% and 44.3% in the late period, respectively. Six patients in the early period survived \( \geq \)5 years and 7 in the late period. This difference in the survival rate between the 2 periods was significant (\( P = 0.0495 \)) (Fig. 3). Excluding the 3 patients who died of postoperative complications and the 9 patients who had pM1 disease, the difference in the survival rate between the 2 periods became even more significant (\( P = 0.0176 \)) (Fig. 4).

**Survival According to the Operative Procedures**

We evaluated the survival impact of right hepatectomy, in the 31 patients with nodular or infiltrating tumor, who tolerated surgery and did not have pM1 disease. Eighteen patients underwent right hepatectomy with caudate lobectomy and the remaining 13 underwent other types of resection (bile duct resection in 9 and less extended hepatectomy in 4).

Bismuth type, histology, tumor progression (pT), and nodal status (pN) were similar in the 2 groups. However, R0 resection was achieved more frequently in patients who underwent right hepatectomy than in those who underwent other types of resection (100% vs. 53.8%, \( P = 0.0023 \)) (Table 3). Probably because of this difference in resectability, survival rate was better in the former than in the latter (5-year survival, 62.9% vs. 23.1%, \( P = 0.0030 \)) (Fig. 5). In the group of other types of resection, all of the 7 patients with Bismuth type I carcinoma underwent bile duct resection without hepatectomy; R0 resection was achieved in only 4 patients (Table 3).

We also evaluated the surgical procedures in the 13 patients with papillary tumor. Of them, 2 patients had pM1 disease (dissemination and para-aortic lymph node metastasis, one each) and the remaining 11 did not. Of the 11 patients, 3 underwent right hepatectomy with caudate lobectomy with (n = 2) or without pancreatoduodenectomy (n = 1) due to superficial spreading. One patient died of liver metastasis and one other died of peritoneal dissemination. The remaining 8 underwent bile duct resection (n = 2) or less extended hepatectomy (n = 6). Despite the fact that right hepatectomy with caudate lobectomy was not performed, all 8 patients underwent R0 resection, and survival was relatively good with a 5-year survival rate of 62.5% (Fig. 6).

**Microscopic Findings of the Resected Right Hepatic Artery**

Extent of right hepatic artery invasion was grade 0 in 19 (95.0%) patients, grade I in 1 (5.0%), and grade II in 0. Of the 19 patients with grade 0 invasion, the distance between the

| TABLE 3. | Comparison of Surgery in Nodular or Infiltrating pM0 Hilar Cholangiocarcinoma |
|-----------------|---------------------------------|---------------------------------|-----------------|
| Left Hepatectomy | Other Types of Resection |
| With Caudate Lobectomy | (n = 18) | Other Types of Resection | (n = 13) |
| Age (yr) | 60.7 ± 10.0 | 59.4 ± 11.1 | 0.72 |
| Gender (male/female) | 8/10 | 9/4 | 0.28 |
| Bismuth type | 5/13 | 7/6 | 0.26 |
| Histologic differentiation | 0.28 |
| Well | 8 (44.4) | 3 (23.1) |
| Moderately or poorly | 10 (55.6) | 10 (76.9) |
| TNM classification | |
| pT | |
| pT1 | 0 | 1 (7.7) |
| pT2 | 7 (38.9) | 5 (38.5) |
| pT3 | 5 (27.8) | 4 (30.8) |
| pT4 | 6 (33.3) | 3 (23.1) |
| pN | 0.25 |
| pN0 | 4 (22.2) | 6 (46.2) |
| PN1 | 14 (77.8) | 7 (53.8) |
| Curability | 0.0023 |
| R0 resection | 18 (100) | 7* (53.8) |
| R1 resection | 0 | 6† (46.2) |

*Values inside parentheses indicate percentages.

*Including 4 patients with Bismuth type I and 3 patients with Bismuth type II.

†Including 3 patients with Bismuth type I and 3 patients with Bismuth type II.
leading edge of the cancer and the outer layer of the adventitia ranged from 0 to 5240 μm, with a median of 500 μm. The distance was <1 mm in 14 (73.7%) of the 19 patients with grade 0 invasion (Fig. 7).

**DISCUSSION**

Bismuth type I and II hilar cholangiocarcinomas appear less advanced on cholangiography and are easier to resect than Bismuth type III and IV tumors. Therefore, many surgeons have chosen local or hilar resections including the extrahepatic suprapancreatic biliary tract as the treatment of choice for Bismuth type I and II tumors. Patients who undergo such limited resection, however, frequently suffer locoregional recurrence, even after formally curative resection, and the prognosis is unexpectedly poor.1,3,4,7 Neuhaus et al1 reported a dismal outcome after hilar resection in 14 patients with Bismuth type I or II tumors. R0 resection was achieved in only 6 (42.9%) patients, and all patients died of recurrence within 5 years. Kondo et al7 also reported a poor prognosis after limited resection. In their series, including 19 patients with Bismuth type I and II tumors, 15 (78.9%) patients underwent limited resection (bile duct resection in 9, isolated caudate lobectomy in 5, and left hepatectomy in 1). Although R0 resection was achieved in most patients, the 3-year survival rate was approximately 15% and only 1 patient survived >3 years. Capussotti et al4 analyzed results of surgery for Bismuth type I and II tumors and found that the long-term outcome was markedly worse in the subset of patients who underwent bile duct resection; none survived more than 2 years. These previous reports indicate that local or hilar resection alone is inadequate for Bismuth type I and II tumors.

On the other hand, there are authors5,6 who recommend right hepatectomy for all Bismuth type I and II tumors. Kawasaki et al6 have stressed the importance of performing right hepatectomy with caudate lobectomy in all patients with Bismuth type I, II, IIIa, and IV tumors, and recommend left hepatectomy only in patients with Bismuth type IIIb. They believe that right hepatectomy offers the best chance of cure in cases of Bismuth type I, II, and IV tumors in which the right and left hepatic ducts are involved to a similar extent. They note the following anatomic considerations:6 first, the extrahepatic part of the left hepatic duct is longer than that of the right hepatic duct; second, the right hepatic artery passes behind the common hepatic duct; therefore, the right hepatic artery is often involved at this site; and, third, systematic caudate lobectomy can be carried out more securely and easily. Although detailed data were not presented in their report, the mean survival for 17 patients with Bismuth type I and II tumors was reported to be 33.7 months6 which is better than reported results of limited resection.1,3,4,7 Seyama et al5 also reported a better prognosis in patients with Bismuth type I and II tumors, who underwent right hepatectomy with caudate lobectomy. In their series, the mean survival for 9 patients with Bismuth type I tumor was 42 months and that for 8 patients with Bismuth type II tumor was 51 months. Considering these favorable results, right hepatectomy seems to confer a survival advantage in patients with Bismuth type I and II tumors.

We had maintained that extrahepatic bile duct resection or the smallest necessary hepatic segmentectomy can be performed after precise evaluation of cancer extent into each segmental bile duct.21,23–25 Through 1996, we performed bile duct resection or less extended hepatectomy in most patients with Bismuth type I and II tumors. As a result, over one-third of resections resulted in R1 or R2 resection, and recurrence was common. All such noncurative resections were associated with nodular or infiltrating tumor. These results imply
that diagnostic imagings, including cholangiography, is not accurate enough to provide precise information about longitudinal extension, as submucosal extension is predominant at the tumor’s proximal border in nodular or infiltrating cholangiocarcinoma. Dissection of the right hepatic artery from tumor, even when macroscopic evidence of invasion is lacking, may have been another cause of the high recurrence rate. Reflecting on this unsatisfactory result, we changed our surgical strategy beginning 1997: right hepatectomy was performed for nodular or infiltrating tumors whenever possible and bile duct resection with or without limited hepatectomy was limited to papillary tumor. Eventually, most patients with nodular and infiltrating tumor underwent right hepatectomy. The incidence of R0 resection was high: excluding resections for patients with pM1 disease, 95.8% (23 of 24) of resections resulted in curative R0 resection, which, in turn, improved long-term survival. Furthermore, in patients with nodular and infiltrating tumor and without pM1 disease, survival was significantly better in patients who underwent right hepatectomy than in those who did not. However, in patients with papillary tumor, survival was fairly good even after local or hilar resection. These observations strongly suggest that our strategy is valid as surgical strategy for Bismuth I and II tumor. A randomized controlled trial is essential to validate this treatment strategy. However, a single center trial is almost impossible because of the very limited number of patients who present this disease, and a multicenter trial has its own difficulties, arising from quality control in diagnosis and actual surgical procedure.

Histologic evaluation of the right hepatic artery showed that invasion of the right hepatic artery is rare, but the distance between the leading edge of the cancer and the outer layer of the adventitia is <1 mm in many cases. This observation suggests that, without combined resection of the right hepatic artery, the margin of resection would have been positive. Therefore, even when invasion of the right hepatic artery cannot be demonstrated preoperatively by diagnostic imagings, right hepatectomy is still recommended.

In conclusion, we recommend that the surgical approach to Bismuth type I and II hilar cholangiocarcinomas should be based on the tumor type seen on the preoperative cholangiogram. For nodular and infiltrating hilar cholangiocarcinomas, right hepatectomy offers the best long-term survival, whereas for papillary tumor, bile duct resection with or without limited hepatectomy is adequate unless extension of superficial cancer spreading is discovered preoperatively.

REFERENCES
Fatty Pancreas
A Factor in Postoperative Pancreatic Fistula

Abhishek Mathur, MD, Henry A. Pitt, MD, Megan Marine, MD, Romil Saxena, MD, C. Max Schmidt, MD, Thomas J. Howard, MD, Attila Nakeeb, MD, Nicholas J. Zyromski, MD, and Keith D. Lillemoe, MD

Objective: To determine whether patients who develop a pancreatic fistula after pancreatoduodenectomy are more likely to have pancreatic fat than matched controls.

Background: Pancreatic fistula continues to be a major cause of postoperative morbidity and increased length of stay after pancreatoduodenectomy. Factors associated with postoperative pancreatic fistula include a soft pancreas, a small pancreatic duct, the underlying pancreatic pathology, the regional blood supply, and surgeon’s experience. Fatty pancreas previously has not been considered as a contributing factor in the development of postoperative pancreatic fistula.

Methods: Forty patients with and without a pancreatic fistula were identified from an Indiana University database of over 1000 patients undergoing pancreatoduodenectomy and matched for multiple parameters including age, gender, pancreatic pathology, surgeon, and type of operation. Surgical pathology specimens from the pancreatic neck were reviewed blindly for fat, fibrosis, vessel density, and inflammation. These parameters were scored (0–4+).

Results: The pancreatic fistula patients were less likely (P < 0.05) to have diabetes but had significantly more intralobular (P < 0.001), interlobular (P < 0.05), and total pancreatic fat (P < 0.001). Fistula patients were more likely to have high pancreatic fat scores (50% vs. 13%, P < 0.001). Pancreatic fibrosis, vessel density, and duct size were lower (P < 0.001) in the fistula patients and negative correlations (P < 0.001) existed between fat and fibrosis (R = −0.40) and blood vessel density (R = −0.15).

Conclusions: These data suggest that patients with postoperative pancreatic fistula have (1) increased pancreatic fat and (2) decreased pancreatic fibrosis, blood vessel density, and duct size. Therefore, we conclude that fatty pancreas is a risk factor for postoperative pancreatic fistula.


PATIENTS AND METHODS

Patient Population

Forty patients who developed a pancreatic fistula, as defined by criteria set by Bassi et al and the International Study Group, were identified from an Indiana University database of over 1000 patients undergoing pancreatoduodenectomies over a 15-year period. Twenty percent of the patients had grade A, 70% grade B, and 10% grade C fistula. Forty patients without a fistula were matched for multiple parameters including age, gender, pancreatic pathology, surgeon, and type of operation. Among these 80 patients, 2

DOI: 10.1097/SLA.0b013e31814a6906
TABLE 1. Patient Population

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Fistula</th>
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<tbody>
<tr>
<td>Age (yr)</td>
<td>63 ± 1.3</td>
<td>61 ± 1.9</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>63</td>
<td>65</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
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<tr>
<td>Pancreatic cancer</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Ampullary cancer</td>
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<td>8</td>
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<tr>
<td>Cystic neoplasm</td>
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<td>6</td>
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<tr>
<td>Duodenal cancer</td>
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<td>4</td>
</tr>
<tr>
<td>Other</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td></td>
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<tr>
<td>BMI (kg/m²)</td>
<td>24 ± 1.2</td>
<td>26 ± 0.8</td>
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<tr>
<td>Hypertension (%)</td>
<td>40</td>
<td>45</td>
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<tr>
<td>Hyperlipidemia (%)</td>
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<tr>
<td>Diabetes (%)</td>
<td>33</td>
<td>13*</td>
</tr>
</tbody>
</table>

*P < 0.05 versus control.

postoperative deaths occurred, and both were a direct result of a pancreatic fistula.

Data for age, gender, diagnosis, and metabolic syndrome for the control and fistula patients are presented in Table 1. The 2 groups were matched for age, gender, and diagnosis. Of the 80 patients, the most common diagnoses were pancreatic cancer in 22 patients, ampullary cancer in 16 patients, cystic neoplasm in 11, and duodenal cancer in 9. Parameters of the metabolic syndrome were recorded including body mass index (BMI) as well as hypertension, hyperlipidemia, and diabetes requiring appropriate medications. The 2 groups did not differ with respect to BMI, hypertension, or hyperlipidemia. The incidence of diabetes was 33% in the control group, which is significantly higher (P < 0.05) than that in the fistula group (13%).

Operations and Surgeons

Operative data are shown in Table 2. One surgeon performed half of the operations, 20 in each group, and 6 surgeons were equally represented in the other half. Pylorus preservation was employed in 75% and 73% of control and fistula patients, respectively. Pancreatojejunostomy was employed in all patients, and all but 2 had a duct-to-mucosa anastomosis. As expected, the mean length of stay was significantly greater for the fistula patients (14 ± 1 vs. 11 ± 1 days, P < 0.05).

TABLE 2. Operative Data

<table>
<thead>
<tr>
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<tr>
<td>Pylorus preservation (%)</td>
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<td>73</td>
</tr>
<tr>
<td>Pancreateojunostomy (%)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Duct-to-mucosa (%)</td>
<td>98</td>
<td>98</td>
</tr>
<tr>
<td>Soft pancreas* (%)</td>
<td>63</td>
<td>68</td>
</tr>
<tr>
<td>Small pancreatic duct (%)</td>
<td>29</td>
<td>80†</td>
</tr>
<tr>
<td>Blood loss (mL)</td>
<td>614 ± 88</td>
<td>736 ± 193</td>
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<tr>
<td>Operative time (min)</td>
<td>290 ± 15</td>
<td>309 ± 32</td>
</tr>
</tbody>
</table>

*Estimated from diagnoses.
†P < 0.001 versus control.

Histologic Analysis

Pancreatic neck specimens were blindly graded (0–4+) for the presence of fat, the degree of fibrosis on hematoxylin and eosin stained slides and for blood vessel density on CD31 stained slides. Figure 1 shows a typical pancreas from a control patient (Fig. 1A) and a fistula patient (Fig. 1B) on hematoxylin and eosin and CD31 stained slides (Figs. 1C, D). A total fat score was calculated for each patient as a sum of the intra- and interlobular fat. CD31-positive blood vessels were counted per 10 high-power fields, and these numbers were converted to a 0–4+ score.

Statistical Analysis

Statistical analyses were performed using Sigma Stat Statistical Software (Jandel Corp., San Rafael, CA). All data are expressed as mean ± SEM. Data were analyzed by using Student t test, Fisher exact test, χ² test and Pearson’s correlation. A P value of less than 0.05 was considered statistically significant.

RESULTS

Pancreatic Fat

Data for intralobular, interlobular, and total fat are presented in Table 3 and Figure 2. All 3 fat parameters were significantly increased in the fistula group and in patients with a small (normal) duct size. Additionally, 50% of the fistula patients and 54% of the patients with small duct size had elevated total fat scores (>3) when compared with only 13% of the controls and 12% of patients with a dilated duct (P < 0.001).

Pancreatic Fibrosis

Data for fibrosis scores and percentage of patients with elevated scores (>2) based on pancreatic leak are presented in Figure 3. The mean fibrosis scores were low in both the control and fistula groups, but the fistula patients had significantly lower scores (P < 0.001). In addition, one-third of the control patients had elevated fibrosis scores (>2) compared with none of the fistula patients (P < 0.001). Moreover, patients with a dilated
duct had elevated fibrosis scores compared with those with a small duct (1.8 ± 0.3 vs. 0.6 ± 0.2, *P* < 0.001). In addition, 44% percent of the patients with a dilated duct had elevated fibrosis scores compared with only 4% with a small duct (*P* < 0.001).

### Vessel Density

Data for blood vessel density and the percentage of patients with elevated scores (≥2) based on pancreatic leak are presented in Figure 4. Vessel density score was significantly lower in the fistula group compared with the

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**FIGURE 1.** A, Typical histology specimen of the neck of the pancreas from a control patient stained with H & E depicting minimal pancreatic fat and slight fibrosis (5×). B, Typical histology specimen of the neck of the pancreas from a fistula patient stained with H & E depicting significant intralobular and interlobular pancreatic fat and minimal fibrosis (5×). C, Typical histology specimen of the neck of the pancreas from a control patient stained with CD31 showing normal vessel density (40×). D, Typical histology specimen of the neck of the pancreas from a fistula patient stained with CD31 showing decreased vessel density in an area of fat (40×).

---

**TABLE 3.** Pancreatic Fat Analysis Based on Control Versus Fistula Groups and Small (Normal) Versus Dilated (Abnormal) Pancreatic Ducts

<table>
<thead>
<tr>
<th></th>
<th>Intralobular Fat Score</th>
<th>Interlobular Fat Score</th>
<th>Total Fat Score</th>
<th>% Patients with Scores &gt;3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control versus fistula groups</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>0.6 ± 0.1</td>
<td>1.4 ± 0.2</td>
<td>1.9 ± 0.3</td>
<td>13</td>
</tr>
<tr>
<td>Fistula</td>
<td>1.5 ± 0.1*</td>
<td>2.0 ± 0.2†</td>
<td>3.5 ± 0.3*</td>
<td>50*</td>
</tr>
<tr>
<td><strong>Small (normal) versus dilated (abnormal)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dilated (abnormal)</td>
<td>0.6 ± 0.1</td>
<td>1.1 ± 0.2</td>
<td>1.7 ± 0.3</td>
<td>12</td>
</tr>
<tr>
<td>Small (normal)</td>
<td>1.5 ± 0.2†</td>
<td>2.1 ± 0.3‡</td>
<td>3.6 ± 0.5†</td>
<td>54°</td>
</tr>
</tbody>
</table>

*P* < 0.001 versus control.
†*P* < 0.05 versus control.
‡ *P* < 0.001 versus dilated.
§ *P* < 0.05 versus dilated.
controls ($P < 0.01$). This trend also was observed with respect to the percentage of patients with a score $\geq 2$, but this difference did not reach statistical significance. In addition, patients with a dilated duct had elevated vessel density scores compared with those with a small duct ($1.9 \pm 0.2$ vs. $1.3 \pm 0.1$, $P < 0.01$). Sixty-seven percent of the patients with a dilated duct had elevated fibrosis scores compared with only 30% with a small duct ($P < 0.001$).

**Correlations of Pancreatic Fat with Fibrosis and Vessel Density**

Correlations of total pancreatic fat with fibrosis and vessel density are presented in Figure 5. Pancreatic fat correlated negatively with fibrosis with a regression coefficient of $-0.40$ ($P < 0.001$). Pancreatic fat also correlated negatively with vessel density with a weaker regression coefficient of $-0.15$ ($P < 0.001$). In addition, fibrosis correlated positively with vessel density with a regression coefficient of $+0.30$ ($P < 0.01$).

**Pancreatic Inflammation**

All the patients showed minimal inflammation. The inflammation scores for the control and fistula groups were $0.2 \pm 0.1$ and $0.1 \pm 0.0$, respectively, and were not significantly different. Similarly, the inflammation scores for patients with a dilated duct and a small duct were $0.2 \pm 0.1$ and $0.1 \pm 0.0$, respectively, and were not significantly different.

**Age, BMI, and Diabetes**

When patients older than and younger than 62 years were compared with each other, no statistical differences in any of the histologic parameters were found. Similarly, no differences were observed in any of the histologic parameters when patients with a BMI greater than and less than 25 kg/m$^2$ were compared. However, BMI correlated positively with total pancreatic fat ($R = 0.13$, $P < 0.001$) and negatively with fibrosis ($R = -0.20$, $P < 0.001$) and vessel density ($R = -0.15$, $P < 0.001$). Data for fat and fibrosis scores in patients with and without diabetes are presented in Figure 6. Intralobular, interlobular, and total pancreatic fat were significantly decreased in patients with diabetes ($P < 0.05$). Fibrosis was significantly increased in patients with diabetes ($P < 0.05$).
No differences were seen with respect to inflammation and vessel density scores in patients with diabetes and those without diabetes.

**DISCUSSION**

From an Indiana University database of over 1000 patients undergoing pancreateoduodenectomy, 40 patients with and 40 patients without a pancreatic fistula were identified and carefully matched for multiple parameters including age, gender, pancreatic pathology, surgeon, and type of operation. Surgical pathology specimens from the pancreatic neck were scored by a blinded observer for fat, fibrosis, vessel density, and inflammation. The control patients were more likely to have diabetes (33% vs. 13%, P < 0.05), and patients with diabetes had significantly (P < 0.05) less fat and more fibrosis in their pancreas compared with those without diabetes. The major new finding was that fistula patients had significantly more (P < 0.001) intralobular, interlobular, and total pancreatic fat. In addition, fistula patients had significantly less (P < 0.001) fibrosis and fewer blood vessels. Additionally, pancreatic fat scores correlated inversely (P < 0.001) with fibrosis and vessel density scores.

Kausch performed the first successful pancreateoduodenectomy for ampullary cancer in 1912. Since then, the indications for pancreateoduodenectomy have grown to encompass a plethora of benign and malignant diseases of the pancreas and peripancreatic region. This increase in the use of pancreateoduodenectomy has been fuelled by decreasing mortality rates with high-volume centers consistently reporting mortality rates less than 4%. However, the morbidity after pancreateoduodenectomy consistently ranges from 40% to 50%, and pancreatic fistula continues to be a problem for many pancreatic surgeons. The risk factors that have been identified for pancreatic fistula formation include a “soft” normal pancreas, a small pancreatic duct, the underlying pancreatic pathology, the local blood flow, and the surgeon’s experience. Therefore, in this analysis, the 2 groups were matched for pancreatic pathology and surgeon, and we tested the hypothesis that pancreatic fat was a risk factor for postoperative fistula. We found that patients with pancreatic fistula were more likely to have an increased amount of pancreatic fat and that fat correlated negatively with both fibrosis and blood vessel density (P < 0.001). Presently, no prospective data are available to correlate the surgeon’s estimate of the texture with the fat content. Therefore, future studies should be designed to capture this information.

A soft texture of the pancreatic parenchyma has been established as a risk factor for fistula development. Increased fat in the pancreas would intuitively increase the softness of the gland. Yeo et al classified the pancreatic texture as noted during operation as hard, intermediate, and soft. They found that the incidence of pancreatic fistula was 0% for patients with a hard pancreas and increased to 25% in patients with a soft pancreas. These findings have been corroborated by Yang et al and Miedema et al. In the present retrospective analysis operative notes were reviewed, but documentation of pancreatic texture was inconsistent. Therefore, we classified the gland into soft and hard on the basis of diagnosis. This surrogate for gland texture was not perfect as matched controls had more fibrosis histologically although their scores were low, averaging only 1.7 on a 4.0 point scale. Conversely, pancreatic fistula patients had significantly more inter- and intralobular fat in their pancreas, which suggests that the presence of fat is more likely in a soft pancreas.

Patients with pancreatic cancer and chronic pancreatitis have increased pancreatic fibrosis and a lower incidence of pancreatic fistula after pancreateoduodenectomy. The protective factors in this observation are believed to be increased fibrosis of the gland and decreased production of pancreatic juice. A fibrotic gland allows for construction of a more secure anastomosis. Friess et al and Uchida et al also have demonstrated that increased fibrosis in pancreatic tissue is associated with decreased exocrine activity. Pancreatic enzymes are believed to play a critical role in proteolytic destruction of the anastomosis. Moreover, activated pancreatic juice is capable of eroding into the surrounding vasculature, which can increase the risk of hemorrhage after the procedure. Therefore, a fibrotic gland which produces fewer pancreatic enzymes is less likely to develop a pancreatic fistula. Our study further reinforces these observations by demonstrating increased histologic fibrosis in the control group.

The best type of pancreatic anastomosis has been a matter of debate. Hosotani et al found that a duct-to-mucosa anastomosis reduced the risk of pancreatic leak. This finding was confirmed by Poon et al who concluded that a duct-to-mucosa anastomosis is safer. The rationale supporting this opinion is that the duct-to-mucosa anastomosis provides a better apposition of the duct to the jejunal mucosa thus reducing leakage of activated pancreatic juice. However, other authors have shown that the type of anastomosis does not influence fistula formation, and randomized studies are needed to answer this question. In

![Fat, Fibrosis and Diabetes](image.png)

**FIGURE 6.** Fat scores (left) and fibrosis scores (right) without (open) and with (crosshatched) diabetes.
this analysis a duct-to-mucosa anastomosis was employed in 98% of the patients. A duct-to-mucosa anastomosis is technically more difficult when dealing with a soft, friable, and fatty pancreas. As a result, some authors have recommended that a pancreas invagination anastomosis should be performed when dealing with a “soft” pancreas.26 The present study suggests that future studies of pancreatic anastomoses should document infiltration by pancreatic fat as well as the texture of the gland.

The other major determinant of a successful anastomosis is the size of the pancreatic duct. A duct size ≤3 mm has been implicated as causative factor in fistula development.16,26 In our study, pancreatic duct size was available in only 28 control and 25 fistula patients. Not surprisingly, from these subsets, 29% of the control patients had a small duct compared with 80% of the fistula patients. Patients with a small duct had elevated fat scores as well as decreased fibrosis and vessel density scores. These observations suggest that a fatty pancreas correlates with a small duct, a known risk factor for pancreatic fistula size. A soft, fatty pancreas with a small duct clearly presents a more technically challenging anastomosis, which is more prone to develop a leak postoperatively.

Strasberg et al first proposed that relative ischemia at the cut surface of the pancreas is a factor in anastomotic failure.17 They suggested that the pancreatic neck is a vascular watershed, which is at increased risk of ischemia when divided. As a result, Strasberg has suggested that the risk of pancreatic fistula can be reduced by cutting back into the pancreatic body if the blood supply is judged by the surgeon to be inadequate. The finding of decreased blood vessel density at the pancreatic neck in patients who developed a pancreatic fistula in the present study confirms Strasberg’s hypothesis. In addition, the negative correlations among fat, fibrosis, and blood vessel density suggest that all 3 factors play a role and that the presence of fat in the pancreas is a risk factor for anastomotic failure.

The factors that have been reported to increase fat infiltration of the pancreas include increasing age, obesity, Cushing syndrome, cystic fibrosis, and lipomatous pseudohypertrophy.1–4,29,30 In this analysis of patients undergoing pancreatoduodenectomy, age greater than or less than 62 years did not correlate with pancreatic fat. However, we matched for age in selecting our controls. When patients with a BMI greater than and less than 25 kg/m² were compared, the fat scores did not differ. However, BMI correlated positively with pancreatic fat and negatively with fibrosis and vessel density (P < 0.001). Kovaniilikaya et al have previously described the role of 3-point Dixon magnetic resonance imaging in tissue fat quantification.3 In addition, Friess et al have outlined the use of the serum panreolauryl test in preoperatively predicting the degree of pancreatic fibrosis.24 Therefore, these modalities, perhaps used in conjunction, may help in determining the risk of developing a pancreatic leak postoperatively and potentially in influencing the operation to be performed. Clearly, further studies need to be designed to test these hypotheses.

In summary, patients with a pancreatic fistula after a pancreatoduodenectomy have more pancreatic fat, less fibrosis, and fewer blood vessels histologically at the pancreatic neck margin. Additionally, pancreatic fat correlates inversely with fibrosis and vessel density and is more likely to be associated with a small pancreatic duct. The presence of increased fat in the pancreas along with a small nondilated duct may make the anastomosis technically more difficult, may be associated with decreased local blood flow, and may increase the risk of perioperative pancreatitis. All these factors may increase the risk of postoperative pancreatic fistula.

Our group has recently defined an animal model of fatty pancreas. We have shown that obese leptin-deficient mice have increased pancreatic total fat, triglycerides, free fatty acids, and cholesterol compared with their lean counterparts. In addition to increased pancreatic lipids, we found an increase in pancreatic tissue interleukin-1β, and tumor necrosis factor-α levels. In addition, both leptin-deficient and leptin-resistant obese mice are more prone to caerulein-induced pancreatitis than lean controls. We have termed this entity nonalcoholic fatty pancreas disease, which can progress to nonalcoholic steatohepatitis under conditions of oxidative stress, similar to the process occurring in nonalcoholic steatohepatitis.34 In the present study, no differences in inflammatory cell infiltrate were seen histologically between the 2 groups. However, adipose tissue has increased cytokines which may be activated by surgical stress causing local pancreatitis, which may enhance fistula formation. This theory is supported by a recent observation that an increase in serum amylase postoperatively is associated with an increase in pancreatic fistula after pancreatectomy.35

Future randomized trials looking at duct-to-mucosa versus dunking anastomosis, stenting versus no stenting, octreotide versus no octreotide, and total versus partial pancreatectomy should monitor the degree of pancreatic fat at the anastomosis. Even though previous trials have been performed, none has monitored the fat content of the pancreas.24,36,37 Kovaniilikaya et al have previously described the role of 3-point Dixon magnetic resonance imaging in tissue fat quantification. In addition, Friess et al have outlined the use of the serum panreolauryl test in preoperatively predicting the degree of pancreatic fibrosis.24 Therefore, these modalities, perhaps used in conjunction, may help in determining the risk of developing a pancreatic leak postoperatively and potentially in influencing the operation to be performed. Clearly, further studies need to be designed to test these hypotheses.

In conclusion, this case–control study suggests that fatty pancreas is another causative factor for postoperative pancreatic fistula after pancreatoduodenectomy.
Right Hepatic Trisectionectomy for Hepatobiliary Diseases

Results and an Appraisal of Its Current Role

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Objective: To assess the results of 275 patients undergoing right hepatic trisectionectomy and to clarify its current role.

Summary Background Data: Right hepatic trisectionectomy is considered one of the most extensive liver resections, and few reports have described the long-term results of the procedure.

Methods: Short- and long-term outcomes of 275 consecutive patients who underwent right hepatic trisectionectomy from January 1993 to January 2006 were analyzed.

Results: Of the 275 patients, 160 had colorectal metastases, 49 had biliary tract cancers, 20 had hepatocellular carcinomas, 20 had other metastatic tumors, and 12 had benign diseases. Fourteen of the 275 patients underwent right hepatic trisectionectomy as part of auxiliary liver transplantation for acute liver failure and were excluded. Concomitant procedures were carried out in 192 patients: caudate lobectomy in 45 patients, resection of tumors from the liver remnant in 57 patients, resection of the extrahepatic biliary tree in 45 patients, and lymphadenectomy in 45 patients. One-, 3-, 5-, and 10-year survivals were 74%, 54%, 43%, and 36%, respectively. Overall hospital morbidity and 30-day and in-hospital mortalities were 41%, 7%, and 8%, respectively. Survival for individual tumor types were acceptable, with 5-year survivals for colorectal metastasis and cholangiocarcinoma being 38% and 32%, respectively. Multivariate analysis disclosed the amount of intraoperative blood transfusion to be the sole independent predictor for the development of hospital morbidity. Age over 70 years, preoperative bilirubin levels, and the development of postoperative renal failure were found to be independent predictors of long-term survival.

Conclusion: Right hepatic trisectionectomy remains a challenging procedure. The outcome is not influenced by additional concomitant resection of tumors from the planned liver remnant. Caution must be taken when considering patients older than 70 years for such resections.


Liver resection remains the mainstay of treatment for neoplastic disease of the liver. The safety and long-term survival results being reported in the literature for hepatic resections are continually improving, mainly as a result of improved surgical techniques and pre-, intra-, and postoperative critical care management of patients. As such, an increasing number of centers are taking more aggressive approaches toward the treatment of patients with primary and secondary hepatobiliary malignancies. Right hepatic trisectionectomy resection of segments 4, 5, 6, 7, 8) was first described by Lortat-Jacob et al as right hepatic lobectomy in 1952, and in detail by Starzl et al as right trisegmentectomy in 1980. The procedure has recently been renamed because of international confusion in nomenclature: terms such as extended right hepatectomy have become ill-defined. It remains a procedure used in few highly specialized units primarily for the treatment of extensive and advanced hepatic or biliary disease. Despite the advances in surgical and anesthetic techniques made in recent years, this procedure is still thought to be associated with higher rates of morbidity and mortality than other resections. This is mainly attributable to the aggressive nature of the (usually malignant) disease being treated, but may also be related to the extent of liver volume being resected, estimated at approximately 80% by several authors. There are, however, no large series that report on the overall and long-term outcomes after right hepatic trisectionectomy, making it extremely difficult to accurately determine the efficacy and safety of this procedure. The objective of this study was therefore to analyze the results of all right hepatic trisectionectomies performed at a single Hepato-Pancreato-Biliary (HPB) unit, and to describe the operative technique used by our surgeons. In addition to assessing long-term outcome, this study also investigates factors affecting morbidity and overall survival, and provides a critical appraisal for the role of right hepatic trisectionectomy in current clinical practice.

Patients and Methods

Between January 1993 and January 2006, 997 liver resections, and 1288 liver transplants were performed in the HPB and Transplant Unit at St James’s University Hospital in Leeds, United Kingdom. The resections were in summary: right-sided hepatectomy, n = 455; left-sided hepatectomy, n = 146; central...
hepatectomy, n = 7; sectionectomy or less n = 389. Of the 997 resection patients, 275 (28%) underwent right hepatic trisectionectomy and were enrolled in this study. There were 162 men and 113 women patients with a mean age of 59.3 (SD 11.72; range, 22–85 years) years. In 11 cases, in situ hypothermic perfusion (n = 5) or ex vivo liver resection (n = 6) techniques were necessary because of tumor extent and the remaining underwent resectional surgery in standard fashion. Fourteen (5%) underwent right hepatic trisectionectomy as part of an auxiliary liver transplant procedure for acute liver failure and these cases are not considered here in detail.

The criteria for acceptance for surgery included fitness for major surgery and lack of disseminated or irresectable extrahepatic disease identified by computerized tomography (CT) scan and potential operability determined by magnetic resonance imaging scan. Examples are shown in Figures 1 and 2. Intraoperative ultrasound was used as an adjunct to the preoperative radiologic investigations. All patients undergoing liver resection for colorectal metastases, according to our unit protocol, were offered adjuvant therapy in the form of 5-fluorouracil/folinic acid, unless they had received adjuvant therapy after their colonic resection within the past 12 months. Because of the historical nature of the data set, relatively few patients received oxaliplatin-based neoadjuvant chemotherapy, and so no attempt has been made to analyze this subset separately. Patients were followed up at specialist clinics, with a minimum follow-up period of 9 months at the time of writing (median, 36 months; range, 9–166 months). No patients were lost to follow-up. An intensive policy of postoperative surveillance exists within this unit. Patients have 3 monthly chest, abdomen, and pelvis CT performed during the first postoperative year, then 6 monthly during year 2. From years 3 to 5, a CT scan is performed yearly and finally at years 7 and 10 of follow-up. Tumor markers (carcinoembryonic antigen, CA19-9) and liver function tests are performed during each clinic visit.

**FIGURE 1.** Magnetic resonance image of a large hepatocellular carcinoma occupying hepatic segments 4 to 8. The left hepatic vein is clearly visible. Segments 2 and 3 are free of tumor. This 49-year-old woman underwent right hepatic trisectionectomy and caudate lobectomy.

**FIGURE 2.** Magnetic resonance images of a large neuroendocrine tumor occupying segments 4 to 8, with involvement of the inferior vena cava, portal vein, and all 3 hepatic veins in a 69-year-old woman. Excision of this tumor required total vascular isolation, ex vivo resection, and reimplantation.
Inevitably, operative techniques have developed with increasing experience. Currently, our technique is as follows. After operability assessment, portal triad dissection is commenced with ligation and division of the cystic duct and artery, allowing access for ligation and division of the right hepatic artery and right portal vein. It is our usual practice to use a surgical stapling device for portal vein transection except in cases of tumor encroachment, where division between vascular clamps and suture ligations may be more appropriate to ensure tumor clearance. Our approach is intra-Glissonian, and no attempt is made to ligate or divide the right hepatic duct at this stage because variant anatomy is common and it is safer to divide the biliary tree later during liver parenchymal transection. Furthermore, we make no attempt to ligate and divide the hepatic artery or portal vein branches to hepatic segment 4 because this is arduous and risks damage to the left hepatic duct. If caudate lobectomy (segment 1 resection) is planned, the left portal vein branches to segment 1 are identified at the base of the umbilical fissure and ligated and divided using fine ligatures. In cases of hilar cholangiocarcinoma, these aspects are preceded by regional or extended (regional + para-aortic) lymphadenectomy along with division of the common bile duct within the superior aspect of the head of the pancreas to allow biliary excision, lymphadenectomy, and neurectomy of the portal triad region. Mobilization of the right liver involves division of the falciform and right triangular ligaments, with ligation of the retrohepatic veins draining the right liver segments into the inferior vena cava. Approximately 30% of patients will require division of a significant (>10 mm) inferior right hepatic vein and in 10% a significant middle right hepatic vein will be found and require division. After division of the peritoneum anterior to the right hepatic vein, this vein is most easily and safely approached from below by dissecting along the inferior vena cava. It can then be divided between vascular clamps or (as is usual in our practice) between surgical staple lines. Further retrohepatic veins (draining segment 4) are then divided to a point where it is possible to feel bimanually the planned hepatic transection plane (posteroanteriorly), determined by tumor extent. This simple maneuver adds considerable safety as it allows vascular control by bimanual pressure if there is difficulty during the subsequent hepatic parenchymal transection. In cases of caudate lobectomy, the dissection is continued from the right across the front of the inferior vena cava (and if necessary from the left side if access from the right is not ideal) with ligation and division of the short veins draining segment 1 into the inferior vena cava, such that the caudate lobe is completely mobilized. Unless there is considerable tumor involvement of segment 1, it can be “flipped” in front of the inferior vena cava, to the right, to allow bimanual palpation of the transection plane, again for vascular control. This “caudate flip” maneuver is usually both simple and helpful in that it speeds up the subsequent liver parenchymal transection. No attempt is made to identify or isolate the middle hepatic vein at this stage as this introduces danger to the left hepatic vein, which almost always has a common insertion into the inferior vena cava with the middle hepatic vein. In some cases it is necessary to divide and reconstruct the major portal and hepatic arterial structures. This is best done after parenchymal transection to gain access for the reconstruction phase, although it can be done before parenchymal transection at this stage if desirable. The only advantage of division of these structures in the umbilical fissure (or just to the left of the fissure in cases of extensive tumor) is a clear line of demarcation at the left edge of segment 4. In the majority of cases this line of demarcation adds little or no advantage. All points of further vascular or biliary division are carried out during parenchymal transection to prevent vascular or biliary

| TABLE 1. Summary of Diseases and Procedures in the 275 Patients Undergoing Right Hepatic Trisectionectomy |
|-----------------------------------------------|------|--------|-------|------|
| Primary liver tumor                          | 54   | S1 43 | EHBD  | MET  |
| Intrahepatic cholangiocarcinoma (%)           | 13   | 6     | 62    | 0    |
| Hilar cholangiocarcinoma (%)                  | 21   | 14    | 67    | 0    |
| Hepatocellular carcinoma (%)                  | 20   | 1     | 5     | 5    |
| Metastatic malignant disease                  | 167  | 12    | 8     | 55   |
| Colorectal (%)                                | 160  | 12    | 8     | 55   |
| Other (%)                                     | 7    | 1     | 14    | 0    |
| Gall bladder cancer (%)                       | 15   | 8     | 62    | 0    |
| GIST (%)                                      | 6    | 1     | 17    | 0    |
| Neuroendocrine (%)                            | 6    | 1     | 17    | 2    |
| Benign liver disease                          | 27   | 1     | 8     | 3    |
| Transplants                                  | 14   | 0     | 0     | 0    |
| Other (%)                                     | 13   | 1     | 8     | 3    |

S4−8 indicates resection of segments 4, 5, 6, 7, 8 only; S1, R Tri + caudate lobectomy; EHBD, extrahepatic bile duct excision + reconstruction; MET, metastasectomy from segments 2, 3; LN, lymphadenectomy; GIST, gastrointestinal stromal tumor (sarcoma).
injury to the residual liver segments (2, 3 ± 1) of the planned liver remnant.

Liver parenchymal transection is done in our center using the CUSA (Valleylab Inc., Boulder, CO) under low central venous pressure anesthesia (<5 cm H₂O), and lifting the left lateral section ventrally (by traction on the round ligament in most cases) to minimize the venous bleeding by reducing the “central venous pressure” within the liver remnant. An intermittent Pringle maneuver is resorted to when necessary, and rarely we have used total vascular isolation. We have not used ischemic preconditioning. Residual vascular and biliary division is done at appropriate stages of the hepatic transection. In cases of perihilar cholangiocarcinoma, it is our usual practice to complete all aspects of the parenchymal transection before division of the segment 2 and 3 hepatic ducts, lifting the extended right liver (segments 4–8), dropping the left lateral section (segments 2 and 3) back to divide the ducts as far away from the tumor as possible. In cases of other primary liver tumors or metastasis, it is our practice to retain the hepatic duct confluence, dividing the segment 1, 4, 5/8, and 6/7 ducts individually to avoid biliary injury. In

<table>
<thead>
<tr>
<th>Grade</th>
<th>n</th>
<th>% of 261 Patients</th>
<th>Cardiopulmonary</th>
<th>Wound Problems</th>
<th>Bile Leak</th>
<th>Infective Bleeding</th>
<th>Liver Dysfunction</th>
<th>Renal Dysfunction</th>
<th>ENC</th>
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<td>I</td>
<td>16</td>
<td>6</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>9</td>
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<tr>
<td>Total</td>
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<td>16</td>
<td>14</td>
<td>10</td>
<td>19</td>
<td>19</td>
<td>25</td>
<td>16</td>
<td>19</td>
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</table>

Totally, 108 patients (41.3%) developed postoperative complications. ENC indicates encephalopathy; Other, ascites, intestinal obstruction, intra-abdominal collections, deep vein thrombosis.

<table>
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<td>S2 + 3 metastasectomy</td>
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<td>42</td>
<td>F</td>
<td>5 November 1995</td>
<td>NK</td>
<td>15</td>
<td>Colorectal</td>
<td>S1</td>
<td>9</td>
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<tr>
<td>5</td>
<td>66</td>
<td>M</td>
<td>4 October 1996</td>
<td>MOD</td>
<td>13</td>
<td>GB cancer</td>
<td>S1, EHBD, LN</td>
<td>2</td>
<td>16</td>
</tr>
<tr>
<td>6</td>
<td>38</td>
<td>M</td>
<td>27 December 1996</td>
<td>MI</td>
<td>19</td>
<td>Cholangio</td>
<td>S1, EHBD</td>
<td>0</td>
<td>500</td>
</tr>
<tr>
<td>7</td>
<td>62</td>
<td>F</td>
<td>30 January 1997</td>
<td>Sepsis</td>
<td>12</td>
<td>GB cancer</td>
<td>EHBD, LN</td>
<td>10</td>
<td>76</td>
</tr>
<tr>
<td>8</td>
<td>76</td>
<td>M</td>
<td>7 March 1997</td>
<td>Sepsis</td>
<td>12</td>
<td>Colorectal</td>
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<tr>
<td>9</td>
<td>74</td>
<td>M</td>
<td>22 May 1998</td>
<td>Sepsis</td>
<td>39</td>
<td>Colorectal</td>
<td>S2 + 3 metastasectomy</td>
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<td>6</td>
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<tr>
<td>10</td>
<td>50</td>
<td>M</td>
<td>12 March 1999</td>
<td>MOD</td>
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<td>11</td>
<td>74</td>
<td>M</td>
<td>8 September 2000</td>
<td>PE</td>
<td>22</td>
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<td>0</td>
<td>13</td>
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<td>12</td>
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<td>F</td>
<td>29 September 2000</td>
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<tr>
<td>13</td>
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<td>GB cancer</td>
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<td>14</td>
<td>72</td>
<td>M</td>
<td>17 September 2001</td>
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<td>Colorectal</td>
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<td>10</td>
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<tr>
<td>15</td>
<td>52</td>
<td>F</td>
<td>20 September 2001</td>
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<td>Colorectal</td>
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<td>5</td>
<td>31</td>
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<tr>
<td>16</td>
<td>75</td>
<td>M</td>
<td>4 November 2001</td>
<td>MOD</td>
<td>12</td>
<td>Cholangio</td>
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<td>4</td>
<td>62</td>
</tr>
<tr>
<td>17</td>
<td>58</td>
<td>M</td>
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<td>MOD</td>
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<td>Colorectal</td>
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<td>0</td>
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<tr>
<td>18</td>
<td>54</td>
<td>M</td>
<td>6 August 2002</td>
<td>MI</td>
<td>4</td>
<td>Esophagus</td>
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<td>0</td>
<td>22</td>
</tr>
<tr>
<td>19</td>
<td>68</td>
<td>M</td>
<td>5 August 2003</td>
<td>MI</td>
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<td>Colorectal</td>
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<td>20</td>
<td>80</td>
<td>M</td>
<td>27 April 2004</td>
<td>MI</td>
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<td>8</td>
<td>13</td>
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<tr>
<td>21</td>
<td>68</td>
<td>M</td>
<td>16 September 2004</td>
<td>Sepsis + MOD</td>
<td>39</td>
<td>Colorectal</td>
<td>None</td>
<td>12</td>
<td>14</td>
</tr>
</tbody>
</table>

DOS indicates date of surgery; COD, cause of death; SUR, survival in days; DIAG, diagnosis; EOP, extraoperative procedure; BT, blood transfusion (units); BILI, bilirubin (µmol/L); MOD, multiple organ dysfunction; Colorectal, colorectal metastases; GB, gallbladder; HCC, hepatocellular carcinoma; Esophagus, esophageal metastases; S, segment; EHBD, extrahepatic bile duct resection; S1, caudate lobectomy; LN, lymph node resection; NK, not known; MI, myocardial infarction; PE, pulmonary embolus; DIC, disseminated intravascular coagulation.
cases with bile duct resection, reconstruction between the left lateral sectional bile duct or the individual segment 2 and 3 bile ducts and the jejunum is performed by Roux-en-Y hepaticojejunostomy.

Preoperative clinical data, operation and pathology reports, postoperative complications, and long-term survival were reviewed. Survivals were calculated using Kaplan-Meier survival charts and compared using log rank testing. Multivariate analysis was performed using Cox logistic regression analysis to determine factors significantly affecting mortality. Binary logistic regression methods were used to assess factors that significantly affect morbidity. A P value less than 0.05 was considered to indicate statistical significance. Statistics were calculated using SPSS 11.0 for Mac OSX.

RESULTS

The majority (91%) of resections were performed for malignant disease. Twelve patients had resections for benign disease and 14 patients had right hepatic trisectionectomies performed during auxiliary liver transplantation. One hundred and forty-seven (54%) patients had resection of segments 4, 5, 6, 7, and 8 only, whereas 45 (16%) patients also had caudate lobe (segment 1) resections, and 37 patients (14%) had extrahepatic biliary tree resection and reconstruction. In 64 patients, it was necessary to resect tumors from the planned hepatic remnant. These results are summarized in Table 1.

All remaining results pertain to the 261 patients undergoing liver resection, excluding the auxiliary liver transplant group. The mean preoperative bilirubin was 34.68 (SD 76.2, range, 2–570 μmol/L) with 22 patients having bilirubin levels of above 75 μmol/L. Tumor size ranged from 10 to 250 mm with a mean of 69.7 mm (SD 50.5). Blood was received intraoperatively or during the first 48 hours postoperatively by 87 patients (33.3%), with the mean transfusion requirement being 2 ± 4 units. The mean Pringle time for the patients who had the maneuver performed was a total of 25 minutes.

Postoperatively, 108 (41%) patients developed complications, summarized in Table 2 according to the novel grading system proposed by Clavien.14,15 Eighteen patients died within 30 days of surgery (7%), and 3 patients died in hospital beyond this time within 90 days, therefore making the in-hospital mortality 8%. One death occurred in the benign disease category in a patient who presented with obstructive and radiologic features of cholangiocarcinoma. Postoperative histology revealed that this patient in fact had histiocytosis X. The patient died of overwhelming sepsis. A summary of the demographic and operative details of these patients is shown in Table 3. There was evidence of reducing mortality with experience (Fig. 3).

One-, 3-, 5-, and 10-year survivals as calculated by Kaplan-Meier survival charts were 74%, 54%, 43%, and 36%, respectively (Fig. 4). Individual disease survivals are shown in and summarized in Table 4. There was no significant difference between the survivals of the malignant diseases on log rank testing (Fig. 5). Disease-free survival for all tumors at 5 years was found to be 43%, with 109 of 261 patients (42%) developing recurrent disease, and the mean disease-free survival time was 2.40 ± 2.82 years.

On univariate analysis, diagnosis of cholangiocarcinoma, preoperative bilirubin levels, amount of blood transfusion, and the number of segments resected (additional resection included caudate lobectomy or complete resection of segment 2 or 3) significantly affected the risk of developing postoperative complications (Table 5). On multivariate analysis of the above factors, intraoperative blood transfusion was found to be the only significant factor affecting morbidity (Table 6). Factors that significantly affected overall survival on univariate analysis were the diagnosis of cholangiocarci-
noma (and to a lesser extent colorectal metastases), age at time of surgery, preoperative bilirubin levels, intraoperative transfusion requirements, the number of procedures performed, and the development of renal failure and sepsis postoperatively (Table 7). Interestingly, we found that resecting metastases from the liver remnant (segments 2 and 3) of patients with colorectal liver metastases did not significantly worsen the survival of these patients when compared with patients who did not need metastasectomies (Table 7, Fig. 6). On multivariate analysis of the above factors, age, preoperative bilirubin, and development of renal failure were all found to be significant independent predictors of overall survival (Table 8).

**DISCUSSION**

Liver resection is now the mainstay of treatment of hepatic and biliary malignancy. With the fall in mortality rates and the acceptance of surgery as a potential cure for such disease, some centers have progressed to routinely performing extensive resections to ensure disease eradication. Although right hepatic trisectionectomy is a well-established procedure, few large case series exist in the literature that report on the efficacy and long-term outcomes in patients undergoing such major surgery. The literature is limited to several small reports describing the use of right hepatic trisectionectomy for treatment of specific malignancy in a handful of patients, or as part of studies describing collective experience of liver resections in certain units.4–8,16–24

The operative techniques we have adopted are simplified, compared with previous descriptions, and have been developed for efficiency and safety. Nagino et al have recently described “anatomic” right hepatic trisectionectomy with caudate lobectomy for hilar cholangiocarcinoma.19

![FIGURE 4. Kaplan-Meier survival curve for all 261 patients undergoing right hepatic trisectionectomies.](image)

**TABLE 4. Summary Number of Patients at Risk of 1-, 3-, and 5-Year Survivals per Disease Category**

<table>
<thead>
<tr>
<th>Diagnosis (No. Entering)</th>
<th>Number at Risk</th>
<th>1-yr Survival</th>
<th>3-yr Survival</th>
<th>5-yr Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal (160) (%)</td>
<td></td>
<td>120 (78)</td>
<td>65 (52)</td>
<td>37 (38)</td>
</tr>
<tr>
<td>Cholangiocarcinoma (35) (%)</td>
<td></td>
<td>18 (58)</td>
<td>10 (42)</td>
<td>7 (32)</td>
</tr>
<tr>
<td>HCC (20) (%)</td>
<td></td>
<td>13 (65)</td>
<td>6 (46)</td>
<td>5 (46)</td>
</tr>
<tr>
<td>Gall bladder cancer (15) (%)</td>
<td></td>
<td>7 (50)</td>
<td>4 (40)</td>
<td>3 (40)</td>
</tr>
<tr>
<td>Neuroendocrine (6) (%)</td>
<td></td>
<td>6 (100)</td>
<td>6 (100)</td>
<td>4 (100)</td>
</tr>
<tr>
<td>GIST (6) (%)</td>
<td></td>
<td>6 (83)</td>
<td>6 (83)</td>
<td>4 (63)</td>
</tr>
<tr>
<td>Other malignant (7) (%)</td>
<td></td>
<td>4 (65)</td>
<td>2 (54)</td>
<td>2 (54)</td>
</tr>
<tr>
<td>Benign (12) (%)</td>
<td></td>
<td>12 (92)</td>
<td>12 (92)</td>
<td>8 (92)</td>
</tr>
</tbody>
</table>

HCC indicates hepatocellular carcinoma; GIST, gastrointestinal stromal tumor (sarcoma).

![FIGURE 5. Kaplan-Meier survival curves according to disease.](image)
Here, the authors stress the importance of careful surgical technique in ligating the portal vein branches to segment 4 before parenchymal transaction. We have not routinely employed this technique, although it has proved useful in some cases where portal vasculature has been compromised. In most of right hepatic trisectionectomy cases, this arduous technique is not necessary, although it may have more application for hilar cholangiocarcinoma.

The largest case number of right hepatic trisectionectomies performed comes from the Memorial Sloan Kettering Cancer Center, which reported on 1001 liver resections performed for colorectal liver metastasis over a 13-year period that included 188 extended right lobectomies.25 However, the

### TABLE 5. Univariate Analysis of Factors Affecting Morbidity

<table>
<thead>
<tr>
<th>Preop. variables</th>
<th>P</th>
<th>Hazard Ratio (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;70 (n = 214)</td>
<td>0.328</td>
<td>1.372 (0.728–2.585)</td>
</tr>
<tr>
<td>&gt;70 (n = 47)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F (n = 111)</td>
<td>0.576</td>
<td>0.868 (0.528–1.427)</td>
</tr>
<tr>
<td>M (n = 150)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholangiocarcinoma (n = 34)</td>
<td>0.012*</td>
<td>3.010 (1.269–7.139)</td>
</tr>
<tr>
<td><strong>Jaundice</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bili &lt;75 (n = 194)</td>
<td>0.05*</td>
<td>2.441 (0.978–6.091)</td>
</tr>
<tr>
<td>Bili &gt;75 (n = 22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>No. segments removed</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solitary (n = 94)</td>
<td>0.375</td>
<td>0.776 (0.443–1.359)</td>
</tr>
<tr>
<td>Multiple (n = 109)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Size of largest tumor</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10 cm (n = 170)</td>
<td>0.462</td>
<td>0.734 (0.322–1.673)</td>
</tr>
<tr>
<td>&gt;10 cm (n = 29)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Intraop. variables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood transfusion (units)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;4 (n = 190)</td>
<td>0.001*</td>
<td>2.887 (1.523–5.473)</td>
</tr>
<tr>
<td>&gt;4 (n = 51)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>No. procedures</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R Tri only (n = 125)</td>
<td>0.06</td>
<td>1.615 (0.984–2.650)</td>
</tr>
<tr>
<td>R Tri ++ (n = 134)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>No. segments removed</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 (n = 212)</td>
<td>0.05*</td>
<td>1.870 (0.999–3.499)</td>
</tr>
<tr>
<td>&gt;5 (n = 49)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Colorectal metastasis</strong></td>
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<tr>
<td>R Tri (n = 104)</td>
<td>0.824</td>
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<tr>
<td>R Tri + metastasectomy (n = 55)</td>
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<td></td>
</tr>
</tbody>
</table>

*Significant.

Bili indicates bilirubin (μmol/L); R Tri, right hepatic trisectionectomy; ++, with extra procedures; >5, caudate lobectomy or complete resection of segment 2 or 3 in addition to right hepatic trisectionectomy; Metastasectomy, tumor resection from planned liver remnant (segments 2 + 3).

### TABLE 6. Multivariate Analysis of Factors Affecting Morbidity

<table>
<thead>
<tr>
<th>Cholangiocarcinoma</th>
<th>P</th>
<th>Hazard Ratio (CI)</th>
</tr>
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<tbody>
<tr>
<td>0.138</td>
<td>2.464</td>
<td>(0.748–8.120)</td>
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<tr>
<td>Preop. bilirubin &gt;75 μmol/L</td>
<td>0.313</td>
<td>1.847 (0.560–6.087)</td>
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<tr>
<td>Blood transfusion &gt;3 units</td>
<td>0.012*</td>
<td>2.568 (1.225–5.380)</td>
</tr>
<tr>
<td>No. segments removed &gt;5</td>
<td>0.526</td>
<td>1.314 (0.565–3.053)</td>
</tr>
</tbody>
</table>

*Significant.

### TABLE 7. Univariate Analysis of Factors Affecting Overall Survival

<table>
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<tr>
<th>Preop. variables</th>
<th>P</th>
<th>Hazard Ratio (CI)</th>
</tr>
</thead>
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<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;0 (n = 212)</td>
<td>0.001*</td>
<td>1.884 (1.280–2.771)</td>
</tr>
<tr>
<td>&gt;70 (n = 47)</td>
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</tr>
<tr>
<td><strong>Gender</strong></td>
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<td></td>
</tr>
<tr>
<td>F (n = 111)</td>
<td>0.958</td>
<td>0.991 (0.711–1.381)</td>
</tr>
<tr>
<td>M (n = 150)</td>
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<td><strong>Diagnosis</strong></td>
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<td></td>
</tr>
<tr>
<td>Other (n = 66)</td>
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<tr>
<td>Colostronic (n = 160)</td>
<td>0.01*</td>
<td>1.808 (1.156–2.828)</td>
</tr>
<tr>
<td>Cholangiocarcinoma (n = 34)</td>
<td>0.002*</td>
<td>2.710 (1.395–4.519)</td>
</tr>
<tr>
<td><strong>Jaundice</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bili &lt;75 (n = 193)</td>
<td>0.006*</td>
<td>2.088 (1.229–3.545)</td>
</tr>
<tr>
<td>Bili &gt;75 (n = 22)</td>
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</tr>
<tr>
<td><strong>No. tumors</strong></td>
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<td></td>
</tr>
<tr>
<td>Solitary (n = 94)</td>
<td>0.686</td>
<td>1.138 (0.747–1.559)</td>
</tr>
<tr>
<td>Multiple (n = 109)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Size of largest tumor</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10 cm (n = 151)</td>
<td>0.532</td>
<td>1.146 (0.748–1.754)</td>
</tr>
<tr>
<td>&gt;10 cm (n = 48)</td>
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<td></td>
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<td><strong>Intraop. variables</strong></td>
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<tr>
<td>Blood transfusion (units)</td>
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<td></td>
</tr>
<tr>
<td>&lt;4 (n = 190)</td>
<td>0.006*</td>
<td>1.743 (1.174–2.586)</td>
</tr>
<tr>
<td>&gt;4 (n = 51)</td>
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<tr>
<td><strong>No. procedures</strong></td>
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<td></td>
</tr>
<tr>
<td>R Tri only (n = 125)</td>
<td>0.04*</td>
<td>1.427 (1.025–1.998)</td>
</tr>
<tr>
<td>R Tri ++ (n = 134)</td>
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</tr>
<tr>
<td><strong>No. segments removed</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 (n = 212)</td>
<td>0.254</td>
<td>1.274 (0.847–1.918)</td>
</tr>
<tr>
<td>&gt;5 (n = 49)</td>
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<td></td>
</tr>
<tr>
<td><strong>Colorectal metastasis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R Tri (n = 104)</td>
<td>0.076</td>
<td>1.453 (0.962–2.197)</td>
</tr>
<tr>
<td>R Tri + metastasectomy (n = 55)</td>
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</tr>
<tr>
<td><strong>Postop. variables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver failure (n = 36)</td>
<td>0.217</td>
<td>1.334 (0.845–2.106)</td>
</tr>
<tr>
<td>Sepsis (n = 18)</td>
<td>0.002*</td>
<td>2.486 (1.401–4.412)</td>
</tr>
<tr>
<td>Bleeding (inc GI bleed) (n = 18)</td>
<td>0.227</td>
<td>1.408 (0.768–2.413)</td>
</tr>
<tr>
<td>Renal failure (n = 15)</td>
<td>0.001*</td>
<td>2.718 (1.498–4.932)</td>
</tr>
</tbody>
</table>

*Significant.

Bili indicates bilirubin (μmol/L); R Tri, right hepatic trisectionectomy; ++, with extra procedures; >5, caudate lobectomy or complete resection of segment 2 or 3 in addition to right hepatic trisectionectomy; Metastasectomy, tumor resection from planned liver remnant (segments 2 + 3); GI, gastrointestinal.
It is important to note, however, that survival rates quoted in the literature for these diseases have usually included patients who underwent relatively minor resections. Rui et al.20 evaluated the role of right hepatic trisectionectomy in 33 patients with primary liver malignancy, 31 of whom had hepatocellular carcinoma. All the patients were Child-Pugh stage A at the time of surgery, and 24% of the patients were reported as having “slight cirrhosis” preoperatively. The 5-year survival for this study was 34.4% compared with 46% in our study. This difference cannot be explained by cirrhosis alone because 15% of our patients were cirrhotic (3 of 20) at the time of resection.

Preoperative jaundice and amount of blood transfusion requirements have been shown to significantly affect mortality in previous studies, including our own.25-27,37 The largest existing series of left trisectionectomy also comes from our unit,39 and when comparing the morbidity, mortality, and long-term survival between the 2 procedures, we find that they are virtually identical. The morbidity rate was slightly better for right hepatic trisectionectomy patients (41% vs. 46%), with the most frequently occurring complication being transient liver insufficiency with hepatic encephalopathy in both studies. The 30-day mortality was also similar in both patient groups at 7%; however, the major cause of death in the left trisectionectomy group was liver and renal failure, whereas cardiovascular complications dominated in the right hepatic trisectionectomy group. This can be explained partly by the age of the patients, with the mean age of those in the right hepatic trisectionectomy group who died within 30 days being 64 ± 10.1 year, and that of the left trisectionectomy

exact nature of the procedure performed by the authors during extended right lobectomy with respect to ligation of the middle hepatic vein is not mentioned, adding weight to the argument for improved nomenclature.9 In addition, Fong et al did not stratify outcomes according to the type of resection performed, and therefore, did not analyze the long-term results of right hepatic trisectionectomy.25 Iwatsuki and Starzl reported on their experience with 411 resections of which 126 were right hepatic trisectionectomies.26 The postoperative mortality in this study was 6%. However, long-term survival for patients undergoing right hepatic trisectionectomies alone was not mentioned. There is limited data in the literature pertaining to predictors of morbidity and overall survival after right hepatic trisectionectomy.

Patients undergoing right hepatic trisectionectomies usually have more aggressive and widespread tumors than those undergoing conventional hepatectomies, thus necessitating the removal of very large liver volumes and ligation of both the right and middle hepatic veins. Despite this, the overall results of right hepatic trisectionectomy in our unit are favorable. The relatively high morbidity rates we experienced are expected, as the patients had lost large liver volumes and were therefore more prone to developing complications. In addition, the complication rates quoted in patients undergoing liver resections in the literature are comparable at 30% to 50%.15,25-36 Our complication rate of 41% in a subset undergoing major resection is therefore acceptable. The 1-, 3-, 5-, and 10-year survivals in our study are good despite the complications encountered. Also favorable was the disease-free survival, with half the patients in the study being alive and disease-free at 3.5 years. The postoperative mortality rate seems relatively high at 8%, with figures quoted in the literature ranging between 3% and 8%.17-19,25-26. It is important to note, however, that 18 of the 21 patients who died did so before 2002 and no in-hospital deaths occurred in the last 2 years (Fig. 3). In addition, the majority of the deaths (9 of 21) were due to cardiorespiratory events, and not from intra-abdominal complications, despite aggressive preoperative cardiorespiratory testing that included echocardiography and stress testing. These data suggest that this degree of liver resection considerably increases cardiac workload in the perioperative period.

The use of portal vein embolization before extensive liver resection to allow hypertrophy of the expected liver remnant has been advocated.17,24 Nagino et al reported on 240 patients with biliary malignancy who underwent portal vein embolization before “extended” right or left hepatectomy.17 They report a perioperative mortality of 8.8%, and 3- and 5-year survivals of 41.7% and 26.8% in cholangiocarcinoma and 25.3% and 17.1% in gallbladder cancer. We did not use portal vein embolization in any of our patients, and achieved similar postoperative mortality and superior 3- and 5-year survivals for cholangiocarcinoma and gallbladder cancer, although our numbers for these diseases are small. Furthermore, we use no scientific tests designed to judge hepatic reserve. In our unit, we have an advantage in that we deal with a northern European population, with a low rate of viral hepatitis, and hence low rates of cirrhosis (1% in this study), although alcoholism is becoming an increasing feature within our practice and we are dealing with more elderly patients than in the past, and more who have undergone neoadjuvant chemotherapy.37 Our experience with cirrhotic patients is therefore small and this may explain our success without the use of portal vein embolization. This is supported by the findings of Farges et al who showed that portal vein embolization did not alter the postoperative outcomes in patients with normal liver parenchyma undergoing right hemihepatectomy.28 In addition, we have found in our practice that tumor replacement of right liver parenchyma often results in hypertrophy of the left lobe, which again may explain our success without the use of portal vein embolization.

Individual survival rates for colorectal liver metastases, cholangiocarcinoma, and hepatocellular carcinoma are comparable to survival rates quoted for these diseases in the literature. It is important to note, however, that survival rates quoted in the literature for these diseases have usually included patients who underwent relatively minor resections. The overall results of right hepatic trisectionectomy in our unit are favorable. The relatively high morbidity rates we experienced are expected, as the patients had lost large liver volumes and were therefore more prone to developing complications. In addition, the complication rates quoted in patients undergoing liver resections in the literature are comparable at 30% to 50%.15,25-36 Our complication rate of 41% in a subset undergoing major resection is therefore acceptable. The 1-, 3-, 5-, and 10-year survivals in our study are good despite the complications encountered. Also favorable was the disease-free survival, with half the patients in the study being alive and disease-free at 3.5 years. The postoperative mortality rate seems relatively high at 8%, with figures quoted in the literature ranging between 3% and 8%.17-19,25-26. It is important to note, however, that 18 of the 21 patients who died did so before 2002 and no in-hospital deaths occurred in the last 2 years (Fig. 3). In addition, the majority of the deaths (9 of 21) were due to cardiorespiratory events, and not from intra-abdominal complications, despite aggressive preoperative cardiorespiratory testing that included echocardiography and stress testing. These data suggest that this degree of liver resection considerably increases cardiac workload in the perioperative period.

The use of portal vein embolization before extensive liver resection to allow hypertrophy of the expected liver remnant has been advocated.17,24 Nagino et al reported on 240 patients with

### TABLE 8. Multivariate Analysis of Factors Affecting Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>P</th>
<th>Hazard Ratio (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;70 yr</td>
<td>&lt;0.001*</td>
<td>2.227 (1.436-3.453)</td>
</tr>
<tr>
<td>Preop. bilirubin &gt;75 μmol/L</td>
<td>0.002*</td>
<td>2.534 (1.421-4.516)</td>
</tr>
<tr>
<td>Intraop. blood transfusion &gt;3 units</td>
<td>0.200</td>
<td>1.336 (0.858-2.078)</td>
</tr>
<tr>
<td>Postop. sepsis</td>
<td>0.241</td>
<td>1.507 (0.759-2.990)</td>
</tr>
<tr>
<td>Postop. renal failure</td>
<td>0.009*</td>
<td>2.614 (1.265-5.400)</td>
</tr>
</tbody>
</table>

*Significant.
group being 56 ± 6.26 years. In both series, the preoperative serum bilirubin proved to be an important factor, with a significant impact on postoperative morbidity after left hepatic trisectionectomy, and mortality after right hepatic trisectionectomy. Caution should be taken, therefore, even in patients with low levels of jaundice.

A previous study by our unit evaluating extensive liver resections in elderly patients did not find that age was a predictor of mortality. Resections were considered extensive if 3 or more segments were resected. In addition, elderly patients undergoing left trisectionectomy in our unit’s experience were not found to be at a higher risk of death. In this study of right hepatic trisectionectomy and another study of liver resection by Alfieri et al, age was found to be an independent predictor of mortality. The discrepancy between our previous study and the current study may be explained by the extent of liver parenchyma resected. When compared with left trisectionectomy, a larger volume of functional liver parenchyma is removed in right hepatic trisectionectomy, so this may account for the emergence of age as an independent predictor of mortality. It seems sensible to suggest that caution must be taken when considering patients above 70 years of age for very major liver resection.

Postoperative liver dysfunction was not found to be a predictor of overall survival on univariate analysis; however, renal failure was a highly positive predictor of overall survival on both univariate and multivariate analysis. This may be explained by the fact that 11 of the 16 patients who developed renal failure had concomitant liver dysfunction. This suggests that those patients who developed liver dysfunction severe enough to result in renal dysfunction were at the highest risk, thereby explaining the significance of renal failure in our analysis.

Finally, we have previously suggested that it is possible to extend right hepatic trisectionectomy by an in-contiguity or nonanatomic resection of tumors from segments 2 and 3, the planned liver remnant. In that study, we demonstrated a low risk of death and hepatic failure and acceptable medium-term survivals for patients with colorectal liver metastases: 52% at 3 years. This current analysis suggests that, with a greater number of patients and longer follow-up, there is a trend toward a worse survival in this group in the long term (Fig. 6), although operative mortality and morbidity risks remain acceptable. The negative trend has, so far, failed to achieve significance (P = 0.075), and is most probably governed by tumor biology, as we have demonstrated recently.

In conclusion, this is the largest study to assess the outcomes of right hepatic trisectionectomy independently, and provides the longest follow-up for patients undergoing this type of resection. The results show that this right hepatic trisectionectomy remains a challenging procedure. The outcome is not significantly influenced by additional concomitant resection of tumors from the planned liver remnant. Caution must be taken when considering patients above 70 years of age for such resections.

REFERENCES


Is Total Parathyroidectomy the Treatment of Choice for Hyperparathyroidism in Multiple Endocrine Neoplasia Type 1?

Francesco Tonelli, MD,* Tommaso Marcucci, MD,* Geri Fratini, MD,* Maria Silvia Tommasi, MD,* Alberto Falchetti, MD,†‡ and Maria Luisa Brandi, MD, PhD†‡

Objective: The aim of the present report is to describe the results obtained with total parathyroidectomy (TPTX) guided by rapid intraoperative parathyroid hormone (PTH) evaluation, followed by immediate parathyroid autograft with fresh tissue.

Summary Background Data: Surgery for hyperparathyroidism (HPT) in multiple endocrine neoplasia type 1 (MEN1) is performed with various surgical approaches.

Methods: We report our 16-year experience of surgical treatment of 51 MEN1-HPT patients using TPTX and thymectomy. Forty-five patients underwent TPTX as the first surgical procedure, whereas for 6 patients, a parathyroid operation was the second surgical procedure. PTH intraoperative values less than 10 pg/mL, at the end of the surgery, were indicative for reimplantation of a few fragments (~1/7) of fresh parathyroid tissue in the brachioradial muscle of the forearm. Parathyroid autograft was performed in all patients, except 3 in whom the fourth parathyroid gland was not found.

Results: Persistent hypoparathyroidism occurred in 13 patients (25%), with higher incidence in patients undergoing a second surgical revision for cervical recurrence than in patients submitted to the first surgery. At follow-up, 5 recurrences (~10%) in the forearm were observed after a mean time of 7 ± 5 (M ± SD) years. No cervical recurrence was documented. The forearm recurrence was treated with removal of 1 or 2 enlarged fragments obtaining the resolution of HPT in all but 1 case.

Conclusions: Based on the occurrence of complications in our experience, TPTX followed by autograft and guided by intraoperative PTH monitoring represents a better surgical option in MEN1-HPT compared with other surgical approaches.

Primary hyperparathyroidism (HPT) is the most common endocrine disorder in multiple endocrine neoplasia type 1 (MEN1), with a penetrance of nearly 100% at age 50 and an age of onset at 20 to 25 years. MEN1-HPT is generally sustained by a multiglandular parathyroid disease with a clonal asymmetric and asynchronous enlargement of all of the parathyroid glands.

Surgery is the elective therapeutic approach to MEN1-HPT and must satisfy the following requirements: 1) to permanently correct the hypercalcemia; 2) to avoid permanent hypocalcemia; and 3) to facilitate a future surgery of possible recurrences. Various surgical approaches have been proposed: 1) less than subtotal parathyroidectomy (LSPTX) with removal of only the enlarged glands; 2) subtotal parathyroidectomy (SPTX) with removal of at least 3 to 3 1/2 glands; and 3) total parathyroidectomy (TPTX) with removal of all parathyroid glands and autologous parathyroid tissue graft.

The results about the operation of choice and the optimal surgical approach are still controversial. The criticisms about TPTX followed by autotransplantation are based on a higher incidence of permanent hypoparathyroidism when compared with the other procedures and are probably related to the use of cryopreserved parathyroid tissue.

The aim of the present report was to describe the results obtained with TPTX, guided by the rapid intraoperative parathyroid hormone (PTH) evaluation and immediately followed by parathyroid autograft with fresh tissue when the values of intraoperative PTH were consistent with a curative surgery.

PATIENTS AND METHODS

From 1990 to 2006, 51 patients with MEN1-HPT (34 women, 17 men; mean age, 38 years; range, 16–69 years) have been treated surgically from the same operator (F.T.) with the intent to perform TPTX. In all patients, MEN1 genetic diagnosis was performed either by linkage or by mutational analysis. The first clinical manifestation of MEN1 syndrome was HPT (52%), hyperprolactinemia (32%), hypergastrinemia (Zollinger-Ellison syndrome) (20%), hyperinsulinemia (9%), and hyperglucagonemia (2%). Forty-five patients underwent TPTX and thymectomy as the first surgical procedure.
Six other patients, previously operated in other institutions, were submitted to neck reexploration (secondary parathyroid operation). Four of these patients were affected by neck recurrent HPT and 2 by neck persistent HPT (Table 1). The previous surgical procedures were SPTX and LSPTX in 2 and 4 patients, respectively. No thymectomy has been previously performed in these patients. One of these patients was previously operated by left thyroid lobectomy for thyroid adenoma. In all of these patients, an accurate evaluation of the residual parathyroid glands was done by instrumental examinations (echo-color Doppler ultrasonography, cervical and mediastinal scintigraphy by Tc-99m sestamibi, Tc-99m MIBI, or double tracer, computed tomography, selective cervical and mediastinal venous catheterization with venous sampling for PTH measurement and evocation of Casanova test). The preoperative mean levels of total calcium and PTH are reported in Table 1.

### Surgical Technique

The surgery encompassed a cervical collar incision, the identification and isolation of inferior laryngeal nerves, and the removal of all the recognized parathyroids, with histologic confirmation of the specimens. Efforts were made to recognize ectopic and/or supernumerary glands by wide bilateral cervical exploration, resection of fatty tissue from the central neck compartment, and transcervical thymectomy. The dimensions of the parathyroid glands have been measured in cubic M Volume $r_1^3 r_2^3 r_3^3$ (normal range: 0.03–0.15 cm³; Fig. 1).12 Fragments of parathyroid tissue of about 1 mm³ in volume each one have been obtained from the most normal appearing gland and immediately placed in sterile lactated Ringer or Wisconsin solution at 4°C. A few fragments (a mean of 7; range, 4–16) have been grafted into separate pockets between the muscular fibers of the brachioradial muscle of the non-dominant forearm. The graft was performed immediately at the end of the operation to use fresh tissue (mean time of ischemia was 65 ± 28 minutes). Parathyroid autograft was performed in all patients, except 3 cases in whom the fourth parathyroid gland was not found. In some patients, thyroid surgery was combined with the parathyroid operation, because of associated thyroid pathology.

### Quick Intraoperative PTH Dosage

In all patients, the quick intraoperative determination of intact parathyroid hormone was performed by immunoradiometric assay (IRMA), and subsequently (since 2000) by immunochemiluminometric assay (ICMA). Sensitivity of IRMA and ICMA is about 10 pg/mL13 and 6 pg/mL, respectively (Quick-Intraoperative intact PTH, Nichols Laboratories, San Juan Capistrano, CA). The circulating PTH concentration was evaluated on peripheral arterial blood samples at the induction of anesthesia (considered as basal level), and subsequently just before and at 10 to 20 minutes after excision of each gland and finally at 30 to 60 minutes after surgery completion. The same blood samples tested for the rapid assessment of PTH were later used for the standard dosage during 24-hour incubation time at room temperature.

### Follow-up

All patients underwent preoperative and postoperative vocal cord inspection. Measurement of serum PTH concentration was performed 24 and 48 hours after surgery. The patients were followed every month for 6 months for the evaluation of recurrence or persistence of HPT. In the case of postoperative hypoparathyroidism, calcium and vitamin D are administered, and the patient is followed every month to adjust the dosages of the therapy. Subsequently, the serum calcium and PTH levels were determined annually, to diag-

### Table 1. MEN 1-HPT 51 Patients

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age Mean (range)</th>
<th>Sex Ratio M/F</th>
<th>Preoperative Total Calcium Mean Levels ± SD (Range [n.v.:2.2–2.6 mmol/L])</th>
<th>Preoperative PTH Mean Levels ± SD (Range [n.v.:10–70 pg/mL])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary surgery</td>
<td>45</td>
<td>40 (16–69)</td>
<td>16/29</td>
<td>2.9 ± 0.5 (2.4–3.3)</td>
</tr>
<tr>
<td>Secondary cervical surgery*</td>
<td></td>
<td></td>
<td></td>
<td>164 ± 50 (80–228)</td>
</tr>
<tr>
<td>For recurrent HPT</td>
<td>4</td>
<td>32 (27–37)</td>
<td>1/3</td>
<td>2.8 ± 0.3 (2.7–3)</td>
</tr>
<tr>
<td>For persistent HPT</td>
<td>2</td>
<td>42 (32–52)</td>
<td>0/2</td>
<td>2.7 (2.6–2.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>*In 4 patients after LSPTX and in 2 patients after SPTX.</td>
</tr>
</tbody>
</table>

FIGURE 1. The volume of the excised parathyroid glands in patients with HPT in MEN1. The volume of the parathyroid glands has been measured in cubic centimeters by the following formula: $(r_1^3 r_2^3 r_3^3) \times \frac{4}{3} \pi$.12
nose recurrent HPT. PTH values were performed in both arms, to determine the gradient between the blood draining the graft-bearing arm and the contralateral arm.

Permanent hypoparathyroidism is defined when the hypocalcemia (serum ionized or albumin-corrected calcium levels below 1.10 or 2.00 mmol/L, respectively) persisted beyond the first postoperative 6 months, necessarily requiring permanent calcium and vitamin D substitution therapy.\(^8\) Persistent HPT occurred if the following parameters were present during the initial 6 months after the operation: 1) reproducible hypercalcemia and elevated or inappropriate PTH levels; and 2) absence of normocalcemic intervals.\(^2\) Recurrent HPT was defined when the calcemia and serum PTH levels increased after 6 months of postoperative normocalcemia.\(^2\) In the case of persistent or recurrent HPT, instrumental exams (Tc-99m sestamibi scan including the neck and the graft arm, echo-color Doppler of neck/forearm and Casanova provocative test) were performed.

The autograft recurrences were treated with removal of macroscopically pathologic fragments, with the support of the rapid intraoperative PTH (ICMA). Complete follow-up data for recurrence and persistence of HPT and permanent hypoparathyroidism were obtained by medical records and telephone interviews with family doctors, patients, and their relatives. Recurrence-free rate was determined by the Kaplan–Meier method.

### RESULTS

Genetic test for \textit{MEN1} gene mutations was performed in 45 patients, and it was negative only in 2 patients. The most frequent type of mutation was the frameshift mutation (51%). Overall at surgery, we found and excised a total of 185 parathyroid glands. The histologic examinations described 156 pathologic parathyroids (84%), with the other parathyroids judged pathologically normal. Twenty-four ectopic glands were found: 21 intrathyemic and 3 in the thyroid. Figure 1 shows that the majority of the removed parathyroids presented with an abnormal volume. In 14 patients (27%), associated thyroid surgery was performed, with total thyroidectomy in 3 patients: 1 affected by thyroid struma, 1 by papillary cancer, and 1 patient with increased values of calcitonin, positive pentagastrin stimulation test, and a preoperative suspicion of medullary thyroid carcinoma (MTC; subsequently diagnosed by histopathology as C cell hyperplasia). In other 4 patients (3 with thyroid struma and 1 with thyroid adenoma) lobectomy of the thyroid gland was performed, whereas nodulectomy in thyroid struma was the treatment of choice in 7 patients (Table 2).

<table>
<thead>
<tr>
<th>Associated Thyroid Pathology</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid Struma</td>
<td>Papillary Cancer</td>
</tr>
<tr>
<td>Lobectomy</td>
<td>3</td>
</tr>
<tr>
<td>Nodular excision</td>
<td>7</td>
</tr>
</tbody>
</table>

#### Quick Intraoperative PTH Measurement

After removal of the parathyroid glands, the intraoperative PTH values at 10/20 minutes were 17 ± 3/11 ± 2 pg/mL and 13 ± 3/6 ± 1 pg/mL (M ± SE), with the IRMA and the ICMA, respectively (Figs. 2A, B).

#### Postoperative Complications

Overall early postoperative complications were observed in 6% of patients. Cervical bleeding was present in 1 patient who underwent primary TPTX associated with total thyroidectomy and central compartment lymphadenectomy for the suspect of MTC. Temporary bilateral recurrent laryngeal nerve palsy was observed in the patient who underwent
neck re-exploration after a previous LSPTX (Table 4). A tetanic crisis developed in a patient operated for recurrent HPT (Table 4). Overall, the results indicate a significant higher percentage of complications after secondary surgery (33%) than what was observed after the first operation (2%) (Table 3). More importantly, no case of permanent recurrent nerve dysfunction was observed.

**Follow-up**

The follow-up of patients who underwent primary and secondary surgery is reported in Table 4. Persistent hypoparathyroidism occurred in 13 patients (25%), with a higher incidence in patients undergoing a second surgical cervical revision than in those who underwent a primary surgery (Table 4). At present in these patients, calcemia is well controlled by substitutive therapy with calcium and calcitriol. At follow-up, 5 recurrences in the forearm were observed (10%) after a mean time of 7 years (Table 4). Recurrence-free rate was in 90% of cases after 10 years (Fig. 3). Four forearm graft recurrences were surgically treated with removal of 1 or 2 enlarged fragments (the mean volume measured was 0.09 cm³ with a range of 0.03–0.15 cm³). The intraoperative PTH values showed a decrease of 50% at least 10 minutes after removal of the enlarged fragments in 3 patients in whom a resolution of HPT was obtained (Fig. 4). On the contrary in 1 patient, in whom the PTH values remained high after the excision of the hyperplastic tissue, a persistence of HPT was observed (curative rate, 80%). No cervical recurrence or persistence of HPT was documented (Table 4). Six patients died during follow-up, none for MEN1-related complications, because 4 deaths were related to cardiovascular causes and 2 deaths were due to a car accident and to pulmonary thromboembolism, respectively.

**DISCUSSION**

Because the best surgical approach to HPT in MEN1 is still controversial,1,2 we reported in this article the results of 16-year experience of TPTX with autotransplantation in our center. The present MEN1 record of TPTX operated patients is the largest derived from a single institution and from a single surgeon to date reported in the literature.

As tumoral parathyroid gland involvement is asymmetric and asynchronous, a marked heterogeneity in gland size is a consistent feature in MEN1 associated HPT.1,7,12,16,17 The failure rate is strongly influenced by the preoperative diagnosis of MEN1, by the surgeon’s experience, by the optimal surgical timing, by the availability of intraoperative diagnostic tools (histologic examination and quick PTH assay), and by the choice of the surgical procedure. All of these variables will be discussed.

First, the preoperative diagnosis of MEN1 syndrome can avoid the erroneous diagnosis of sporadic primary HPT,
Macroscopically, normal parathyroid glands range from 12% to 55% and, therefore, the intraoperative appearance can simulate sporadic HPT, with 1 or more rarely 2 enlarged glands.\textsuperscript{12,16,17,35} In our experience, the parathyroid glandular volume was in the normal range in 16% of the excised parathyroid glands. Moreover, often the recognition of all parathyroid glands can be difficult. In the experience of the French GENEM Group, this happened in about 20% of the patients, whereas in our experience in 7% of the cases. Moreover, the macroscopic appearance of the MEN1 parathyroid glands is confounding, as they can grow with multilobulated or kissing shape, contributing to erroneous interpretations (ie, multilobulated glands may be considered as supernumerary, and kissing-shaped glands may lead to misdiagnosis). In addition, parathyroid tissue in MEN1 is frequently reported as ectopic (13% in our experience), being often intrathymic, within the thyroid gland, in the anterior mediastinum, or exceptionally in the pericardium.\textsuperscript{7,16,36,37} Some reports also described the presence of pathologic parathyroid nests embedded within the fatty tissue surrounding the trachea, the esophagus, the carotid artery, and within the thymic tissue.\textsuperscript{7,36,37} Finally, supernumerary glands are frequently found (up to 20%).\textsuperscript{2,7,17,38} Even though no supernumerary glands were observed in our experience. A possible explanation for this discrepancy is a misinterpretation of heterogeneous size, location, and shapes of the parathyroid glands in MEN1.

Third, the surgical timing is another variable in MEN1-HPT. In asymptomatic cases with mild hypercalcemia, surgery could be postponed to increase the chances to find larger parathyroid glands at surgery. On the other hand, prompt intervention could avoid complications of HPT both at the bone and kidney levels in young patients with MEN1. Indeed, even though MEN1-HPT is often asymptomatic in young subjects, reduced bone mass has been described in patients as early as at 35 years of age.\textsuperscript{39} Moreover, hypercalcemia may affect the secretion of gastrin from gastrin-producing cells, precipitating and/or exacerbating symptoms of Zollinger-Ellison syndrome in patients with MEN1.\textsuperscript{4} At present, accurate investigations of the patients affected with MEN1 enable the easier and earlier diagnosis of HPT and of its complications, making it possible to tailor the optimal surgical time in the single case.

Fourth, intraoperative diagnostic tools could influence the outcome of any surgical approach. The intraoperative histologic examination is necessary to confirm the presence of parathyroid tissue in the removed tissues and this is even truer in doubtful cases, when ectopic or normally appearing glands are found. The histologic examination is also crucial for qualifying the tissue used for autotransplantation, and quick intraoperative PTH measurement has become an important diagnostic tool to guide parathyroid surgery.\textsuperscript{40} Its sensitivity is reported as nearly 95%,\textsuperscript{17,40,41} When used for MEN1-HPT, quick intraoperative PTH has the main role to ascertain the removal of all parathyroid glands, even though the biochemical criteria for a successful TPTX are not universally established. Some authors reported the decrease of PTH values of more than 50% from baseline as a good positive predictive factor of a successful outcome.\textsuperscript{17,41}
observed that this principle can lead to false-positive interpretation of the data for the presence of residual but temporarily suppressed glands. Indeed, in a previous report, we showed that the intraoperative PTH kinetics after removal of the first hyperplastic parathyroid gland during TPTX in patients with MEN1 syndrome was characterized by a decline of PTH levels less significant than the drastic drop in the hormonal levels obtained after the excision of an adenomatous gland in sporadic primary HPT.40 However, the occurrence in 2 patients of that series an adenoma-like pattern of PTH decrease after removal of the first gland can be referred to the presence of 1 hyperfunctioning parathyroid gland that was suppressing all of the other parathyroids.40 We concluded that multiple intraoperative PTH measurements should be performed in MEN1 to follow the progressive PTH decrease over time after the removal of each gland.40 Overall PTH values of about 6 pg/mL or undetectable results by the ICMA represent strong indicators for a successful TPTX.

Finally, the choice of the surgical procedure to be applied is a critical variable with a great impact on the results obtained at different centers. LSPTX is defined by the removal of 2 to 2 1/2 glands, leaving in situ 1 1/2 to 2 unaffected glands, which usually are marked with titanium clips or unabsorbable stitches to make their identification easier in the case of a reoperation for persistent or recurrent HPT. LSPTX is always associated with high persistence/recurrence rates.8,10,11,16,17,38,42–46 This is not surprising in MEN1-HPT, where all the parathyroid tissue is going to be removed at different centers. LSPTX is defined by the resection of only 5 to 10 fragments is accompanied by a high rate of permanent hypoparathyroidism and allows easier surgery in the case of recurrence. Transcervical thymectomy is also helpful in preventing carcinoids that can arise in such organs in MEN1 syndrome.3,55 However, other authors highlight the potential failure of the transcervical approach to resect all thymic tissue and to appropriately treat an existing thymic neoplasia.56

The graft for autotransplantation taken at the end of the operation is used as fresh autologous tissue preserved at 4°C in isotonic solution or as cryopreserved tissue, according to a previously described protocol.9 The tissue to graft should be chosen by the most normal appearing gland in volume, color, and texture, and after histologic confirmation of its nature. Fragments to graft should be small (around 1 mm³) to avoid graft necrosis and to allow their long-term survival.57 The optimal site of the graft is generally represented by the brachioradialis muscle of the nondominant forearm. This makes it possible to easily monitor the effectiveness of the procedure by measuring PTH levels in blood samples from the bilateral basilic veins. The number of fragments to graft is still debated with various reports in the medical literature. In the case of cryopreserved tissue, 20 to 25 fragments or more are considered to be the optimal number, because the implantation of only 5 to 10 fragments is accompanied by a high rate (50%–60%) of nonworking grafts.58,59 In our experience, a correlation between the risk of onset of persistent hypoparathyroidism and the number of grafted fragments was lacking. In fact, the mean number of fragments was 7 in patients affected by persistent hypoparathyroidism and in those who were not. It is still unclear whether the success rate is associated to technical problems or to the intrinsic characteristics of the transplanted parathyroid tissue. Moreover, local microenvironmental factors (ie, angiogenesis) could also influence the outcome of the autograft. Interestingly, a rapid parathyroid functional recovery with no permanent hypoparathyroidism was observed by Jansonn and Tisell after they grafted parathyroid tissue within abdominal subcutaneous fat in 7 patients with MEN1.11

In conclusion, at present TPTX with transcervical thymectomy and autologous graft of parathyroid tissue and SPTX with removal of at least 3 to 3 1/2 glands are both considered acceptable surgical procedures for MEN1-HPT.2,5 Conversely, LSPTX should be avoided, because of the multicentric nature of parathyroid disease in MEN1.7 A randomized prospective trial comparing operative approaches for HPT in MEN1 should certainly help to design universally accepted guidelines. In our experience, TPTX is considered the best approach for the treatment of MEN1-HPT, making possible the removal of all parathyroid tissue and allowing the selection of the tissue to be transplanted. Indeed, the percent of persistent hypoparathyroidism reported in our experience was not different from that reported in SPTX.
surveys. These results could be attributed to the autotransplantation of more viable fresh tissue. In addition, TPTX reduces the risk for recurrent HPT when compared with SPTX, with a cumulative incidence of 10% at 10 years. Finally, in the event of reoperations in the forearm, the curative rate was 80% higher than that obtained by other reports. An important observation derived from our experience is the lack of cervical persistent HPT following parathyroid surgery. Together these results support the role for several variables, including the experience of a dedicated surgical team, in influencing the outcomes of parathyroid surgery in MEN1-HPT.

REFERENCES


Racial Disparities in Clinical and Economic Outcomes From Thyroidectomy

Julie Ann Sosa, MA, MD, Pritesh J. Mehta, BA, Tracy S. Wang, MD, MPH, Heather L. Yeo, MD, and Sanziana A. Roman, MD

Context: Thyroid disease is common, and thyroidectomy is a mainstay of treatment for many benign and malignant thyroid conditions. Overall, thyroidectomy is associated with favorable outcomes, particularly if experienced surgeons perform it.

Objective: To examine racial differences in clinical and economic outcomes of patients undergoing thyroidectomy in the United States.

Design, Setting, Patients: The nationwide inpatient sample was used to identify thyroidectomy admissions from 1999 to 2004, using ICD-9 procedure codes. Race and other clinical and demographic characteristics of patients were collected along with surgeon volume and hospital characteristics to predict outcomes.

Main Outcome Measures: Inpatient mortality, complication rates, length of stay (LOS), discharge status, and mean total costs by racial group.

Results: In 2003–2004, 16,878 patients underwent thyroid procedures; 71% were white, 14% black, 9% Hispanic, and 6% other. Mean LOS was longer for blacks (2.5 days) than for whites (1.8 days, $P < 0.001$); Hispanics had an intermediate LOS (2.2 days). Although rare, in-hospital mortality was higher for blacks (0.4%) compared with that for other races (0.1%, $P < 0.001$). Blacks trended toward higher overall complication rates (4.9%) compared with whites (3.8%) and Hispanics (3.6%, $P = 0.056$). Mean total costs were significantly lower for whites ($5447/patient) compared with those for blacks ($6587) and Hispanics ($6294). The majority of Hispanics (55%) and blacks (52%) had surgery by the lowest-volume surgeons (1–9 cases per year), compared with only 44% of whites. Highest-volume surgeons (>100 cases per year) performed 5% of thyroidectomies, but 90% of their patients were white ($P < 0.001$). Racial disparities in outcomes persist after adjustment for surgeon volume group.

Conclusions: These findings suggest that, although thyroidectomy is considered safe, significant racial disparities exist in clinical and economic outcomes. In part, inequalities result from racial differences in access to experienced surgeons; more data are needed with regard to racial differences in thyroid biology and surveillance to explain the balance of observed disparities.


Thyroid disease is a common problem in the United States. Up to 5% of the general population reports having thyroid disease or require some form of thyroid hormone supplementation secondary to abnormalities in thyroid function.1 The frequency of thyroid nodules increases with age; in autopsy series, patients were found to have occult thyroid nodules in up to 80% of cases. Overall, the lifetime risk of developing thyroid cancer is 1%; an estimated 33,550 new cases of thyroid cancer will be diagnosed in 2007.2–5

Thyroidectomy is a mainstay of treatment for benign and malignant thyroid disease, including Graves disease, toxic and nontoxic nodules, symptomatic goiters, and malignancy. Thyroid surgery is associated with excellent clinical outcomes, including short length of hospital stay and low morbidity and mortality, in the hands of experienced surgeons.

Racial disparities in health care have been well-documented in the literature. Racial and/or ethnic minorities have been shown to have less access to preventative care and surgery; as a result, they may have delayed diagnoses, and thereby more advanced disease at presentation.6–12 The compromised access to care observed among minorities stems in part from socioeconomic factors, as well as cultural differences; these include mistrust among certain minority popula-
tions towards the health care system, the potential lack of multicultural competency among health care providers, and lack of health literacy among certain patients.

Although racial disparities in patient outcomes have been described in cardiovascular disease and malignancies such as breast and colon cancer, there have been scant data looking at differences in survival for thyroid cancer.13 Race and ethnicity as predictors of outcomes from thyroid surgery have not been evaluated to date.7,9,10,12 Our study seeks to measure the effects of race and ethnicity on clinical and economic outcomes after thyroidectomy in patients with benign and malignant diseases of the thyroid.

METHODS

Data Source

This study is a cross-sectional analysis of 2003 and 2004 discharge information obtained from the Health Care Utilization Project National Inpatient Sample (HCUP-NIS) national database, which is maintained by the Agency for Healthcare Research and Quality.14 HCUP-NIS is the largest all-payer inpatient database in the United States; it is a stratified 20% sample of inpatient admissions to acute care
considered using the validated All Patient Refined Diagnosis
and thyroid cancer (all kinds). Patient comorbidity was con-
and multinodular goiters; other benign (adenoma and cyst)
ism, toxic uni- and multinodular goiters, and nontoxic uni-
specified cause, Graves disease, goiters with hyperthyroid-
HMO, self-pay). Patients were assigned a thyroid diagnosis;
income ($1–35,999, $36,000 – 44,999, $45,000 –58,999, and
specified cause, Graves disease, goiters with hyperthyroid-
LOS) (2); total patient costs, adjusted to 2004 dollars (3);
other transfers).
Outcome Variables
Primary outcomes of interest were (1) length of stay
LOS) (2); total patient costs, adjusted to 2004 dollars (3);
in-hospital patient complications (4); in-hospital mortality;
and (5) patient disposition at the time of discharge (routine
discharge, home-health care, transfer to intermediate care,
other transfers).
Total patient costs were calculated by multiplying pa-
tient charges from the NIS discharge records by the specific
NIS-adjusted, hospital-specific cost-to-charge ratios.18 We
then adjusted costs for inflation, converting all 2003 costs to
2004 using an inflation rate from the Bureau of Labor
statistics of 2.7%.19
Based on 15 diagnosis codes (ICD-9) included in the
data, we identified postoperative complications (cardiovascu-
lar, endocrine, gastrointestinal, hematologic/vascular, neuro-
logic, urologic, respiratory, infections, and wound), and com-
lications unique to thyroidectomy (ie, hypoparathyroidism
and recurrent laryngeal nerve injury). Complications were
treated as a binomial outcome (complication vs. no compli-
cation).

Data Analysis
Univariate analysis of the independent variables by our
outcomes of interest was performed by χ²-statistical analysis
for categorical variables and analysis of variance for contin-
uous variables. Multivariate linear regression models were
used to adjust for significant independent variables for LOS
and total in-patient costs, whereas multivariate logistic re-
gression models were used to adjust for independent variables
for in-patient mortality and complications, as well as patient
disposition. Data analysis and management were performed
using SPSS Version 14.0 (Chicago, IL). The NIS is publicly
available and contains no personal identifying information;
therefore, this study was deemed to be exempt from Institu-
tional Review Board approval at our institution.

RESULTS
Patient Characteristics
In 2003 and 2004, 16,878 patients who underwent
thyroid procedures were included in HCUP-NIS. The major-
ity of patients were white (71%); blacks represented 14%,
Hispanics 9%, and other racial groups 6% (Table 2). The
overall mean age of patients who underwent thyroidectomy
was 51 years; by comparison, racial minorities were slightly
younger; mean age of blacks was 50 years, Hispanics 48
years, and others 49 years. White patients were more often
men (31%), with significantly higher median household in-
comes and private insurance or Medicare. Differences by race
were most pronounced for the extreme household income
categories. For example, 35% of white patients who under-
went thyroidectomy were in the highest annual household
income category (≥$59,000), compared with 14% of blacks
and 17% of Hispanics. By comparison, only 16% of white
patients who underwent thyroidectomy were in the lowest
income category (<$36,000), compared with 43% of blacks
and 38% of Hispanics. White patients who underwent thy-
roidectomy were more likely to be insured privately (68%)
than black (58%) and Hispanic patients (56%); Medicaid was
the principal payer for blacks (14%) and Hispanics (18%)~
~much more often than whites (4%). Given the older age
distribution seen for whites, it is not surprising that Medicare
insured more whites (24%) than all other racial groups.

Clinical Characteristics
Clinical characteristics also differed significantly by
racial group (Table 2). Total thyroidectomy was more often
performed among whites (43%) than other groups, whereas

### TABLE 1. ICD-9 Thyroid Procedure Codes

<table>
<thead>
<tr>
<th>ICD-9</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.2</td>
<td>Unilateral thyroid lobectomy</td>
</tr>
<tr>
<td>6.31</td>
<td>Excision of lesion of thyroid</td>
</tr>
<tr>
<td>6.39</td>
<td>Partial thyroidectomy</td>
</tr>
<tr>
<td>6.4</td>
<td>Complete thyroidectomy</td>
</tr>
<tr>
<td>6.50</td>
<td>Substernal thyroidectomy NOS</td>
</tr>
<tr>
<td>6.51</td>
<td>Partial substernal thyroidectomy</td>
</tr>
<tr>
<td>6.52</td>
<td>Complete substernal thyroidectomy</td>
</tr>
</tbody>
</table>
subtotal thyroidectomy was seen more often among blacks and Hispanics (both 57%). Substernal thyroidectomy rates were highest among blacks (6%). Blacks carried a benign diagnosis most commonly (80%), whereas Hispanics had the highest thyroid cancer diagnosis rate (45%).

The majority (73%) of patients undergoing thyroid procedures appeared to be healthy, with only “minor loss of function” based on severity of illness score. In spite of being younger, blacks had the highest percentage (3.7%) of patients in the “major and extreme loss of function” categories, signifying more severe comorbid conditions. By comparison, only 2.3% of white patients were so severely compromised by comorbidities. Accordingly, blacks had a significantly lower proportion of elective admissions for their thyroidectomies (85%) compared with 91% for whites ($P < 0.001$).

### Provider Characteristics

There also were significant geographic and provider differences among the races (Table 3). The United States was divided into 4 regions: Northeast, South, West, and Midwest. Overall, more thyroidectomies were performed in the South (37%) and Northeast (35%) than in any other region. Blacks more commonly underwent their surgery in the South (50%) and Northeast (34%), whereas Hispanics (34%) and other racial groups (36%) more often had thyroidectomies in the

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**TABLE 2. Demographic Characteristics of Patients Who Underwent Thyroidectomy, by Race (HCUP 2003–2004)**

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>White 11,965 (70.9)</th>
<th>Black 2298 (13.6)</th>
<th>Hispanic 1484 (8.8)</th>
<th>Other* 1113 (6.7)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ($\pm$ SEM)</td>
<td>52.0 ($\pm$ 0.14)</td>
<td>50.06 ($\pm$ 0.29)</td>
<td>48.05 ($\pm$ 0.39)</td>
<td>48.94 ($\pm$ 0.44)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>18–44</td>
<td>4004 (34)</td>
<td>849 (37)</td>
<td>642 (43)</td>
<td>447 (40)</td>
<td></td>
</tr>
<tr>
<td>45–64</td>
<td>5175 (43)</td>
<td>1066 (46)</td>
<td>593 (40)</td>
<td>491 (43)</td>
<td></td>
</tr>
<tr>
<td>65–79</td>
<td>2327 (19)</td>
<td>348 (15)</td>
<td>223 (15)</td>
<td>170 (15)</td>
<td></td>
</tr>
<tr>
<td>≥ 80</td>
<td>459 (4)</td>
<td>35 (2)</td>
<td>26 (2)</td>
<td>23 (2)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Women</td>
<td>9504 (79)</td>
<td>1994 (87)</td>
<td>1273 (86)</td>
<td>927 (82)</td>
<td></td>
</tr>
<tr>
<td>Median household income ($)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>1–35,999</td>
<td>1879 (16)</td>
<td>961 (43)</td>
<td>544 (38)</td>
<td>161 (14.4)</td>
<td></td>
</tr>
<tr>
<td>36,000–44,999</td>
<td>2589 (22)</td>
<td>534 (24)</td>
<td>328 (23)</td>
<td>239 (21)</td>
<td></td>
</tr>
<tr>
<td>45,000–58,999</td>
<td>3141 (27)</td>
<td>437 (19)</td>
<td>328 (23)</td>
<td>290 (26)</td>
<td></td>
</tr>
<tr>
<td>59,000 or more</td>
<td>4146 (35)</td>
<td>323 (14)</td>
<td>244 (17)</td>
<td>427 (38)</td>
<td></td>
</tr>
<tr>
<td>Primary payer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Private HMO</td>
<td>8130 (68)</td>
<td>1332 (58)</td>
<td>823 (56)</td>
<td>774 (68)</td>
<td></td>
</tr>
<tr>
<td>Medicare</td>
<td>2910 (24)</td>
<td>486 (21)</td>
<td>226 (15)</td>
<td>158 (14)</td>
<td></td>
</tr>
<tr>
<td>Medicaid</td>
<td>485 (4)</td>
<td>320 (14)</td>
<td>262 (18)</td>
<td>128 (11)</td>
<td></td>
</tr>
<tr>
<td>Self-pay</td>
<td>177 (2)</td>
<td>77 (3)</td>
<td>42 (3)</td>
<td>37 (3)</td>
<td></td>
</tr>
<tr>
<td>No charge</td>
<td>28 (0.2)</td>
<td>27 (1)</td>
<td>63 (4)</td>
<td>7 (0.6)</td>
<td></td>
</tr>
<tr>
<td>Principal procedure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Subtotal thyroidectomy</td>
<td>6318 (53)</td>
<td>1308 (57)</td>
<td>840 (57)</td>
<td>630 (56)</td>
<td></td>
</tr>
<tr>
<td>Complete thyroidectomy</td>
<td>5195 (43)</td>
<td>858 (37)</td>
<td>595 (40)</td>
<td>464 (41)</td>
<td></td>
</tr>
<tr>
<td>Substernal thyroidectomy</td>
<td>452 (4)</td>
<td>132 (6)</td>
<td>49 (3)</td>
<td>37 (3)</td>
<td></td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Benign†</td>
<td>4442 (43)</td>
<td>1282 (65)</td>
<td>495 (39)</td>
<td>391 (40)</td>
<td></td>
</tr>
<tr>
<td>Thyroid cancer</td>
<td>3890 (37)</td>
<td>392 (20)</td>
<td>567 (45)</td>
<td>411 (42)</td>
<td></td>
</tr>
<tr>
<td>Other benign (adenoma and cyst)</td>
<td>2086 (20)</td>
<td>285 (15)</td>
<td>195 (16)</td>
<td>189 (19)</td>
<td></td>
</tr>
<tr>
<td>Severity of Illness (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Minor loss of function</td>
<td>8662 (77)</td>
<td>1627 (75)</td>
<td>1115 (76)</td>
<td>880 (80)</td>
<td></td>
</tr>
<tr>
<td>Moderate loss of function</td>
<td>2327 (21)</td>
<td>468 (21)</td>
<td>311 (21)</td>
<td>207 (19)</td>
<td></td>
</tr>
<tr>
<td>Major loss of function</td>
<td>180 (2)</td>
<td>75 (3)</td>
<td>34 (2)</td>
<td>18 (2)</td>
<td></td>
</tr>
<tr>
<td>Extreme loss of function</td>
<td>36 (0.3)</td>
<td>15 (0.7)</td>
<td>6 (0.4)</td>
<td>4 (0.4)</td>
<td></td>
</tr>
<tr>
<td>Type of admission</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Elective</td>
<td>10,864 (91)</td>
<td>1949 (85)</td>
<td>1293 (88)</td>
<td>1018 (90)</td>
<td></td>
</tr>
</tbody>
</table>

*Other includes, but is not limited to, Asians, Pacific Islanders, and Native Americans.
†Benign includes hyperthyroidism of unspecified cause, Graves disease, goiters with hyperthyroidism, toxic uni- and multinodular goiters, and nontoxic uni- and multinodular goiters.
West. More whites had thyroidectomies in the Midwest (13%) than all other races ($P < 0.001$).

Most patients (96%) had surgery in urban hospitals. Black patients were more likely to have surgery at teaching institutions (67%) than all other races (53%) ($P < 0.001$).

Surgery performing thyroidectomy were classified based on the number of thyroid procedures they performed per year. Lowest-volume surgeons performed 1 to 9 cases per year, whereas highest-volume surgeons performed >100 cases per year. The majority of Hispanic (55%), other (53%), and black (52%) patients had surgery by the lowest-volume surgeons, compared with only 44% of white patients (Fig. 1). A significantly higher proportion of white patients were referred to the highest-volume surgeons than all other race groups; 7% of whites underwent thyroidectomy by surgeons performing >100 cases per year, compared with 2% of blacks, and 1% of Hispanics. Highest-volume surgeons performed 5% of all thyroid procedures, but 90% of their patients were white ($P < 0.001$). The geographic distribution of the highest-volume surgeons varied substantially. More surgeons in this category were located in the Northeast (69%), followed by the Midwest (17%). They were not in the South (0%, $P = 0.001$).

### Patient Outcomes

Mean LOS for thyroidectomy was significantly longer for blacks (2.5 days) than for whites (1.8 days) ($P < 0.001$); Hispanics had an intermediate LOS at 2.2 days (Table 4). Although it was a rare outcome, in-hospital mortality was also highest for blacks (0.4%) compared with that for other races (0.1%) ($P < 0.001$). Blacks had a higher overall complication rate (4.9%) compared with whites (3.8%) and Hispanics (3.6%); this observation approached statistical significance ($P = 0.056$). There was no difference in the rates of hypoparathyroidism and recurrent laryngeal nerve injury by race. The majority of patients underwent routine discharges (98%), but Hispanics required additional home health care/transfers to other facilities more often (2.4%) than the other racial groups (1.7%, $P < 0.01$). Given the observed differences by race in LOS, complications, and mortality, it is not surprising that mean total hospital costs were significantly lower for white patients ($5447/patient) and the other race group ($5479) compared with those for blacks ($6587) and Hispanics ($6294).

These differences in clinical and economic outcomes were robust, in that many persisted even after adjustment for other demographic and clinical characteristics that proved to be independent predictors of outcome based on univariate analyses (Table 5). For example, even after adjusting for age, gender, hospital region, procedure, diagnosis, comorbidity, surgeon volume, household income, primary payer, and admission type, black patients still had longer mean LOS (2.3 days) than whites (1.7 days), Hispanics (2.2 days), and the other racial group (1.7 days), as well as significantly higher

### Table 3. Provider Characteristics of Thyroidectomy Patients, by Race (HCUP 2003–2004)

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>White (11,965; 70.9)</th>
<th>Black (2298; 13.6)</th>
<th>Hispanic (1484; 8.8)</th>
<th>Other (1131; 6.7)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geographic region</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Northeast</td>
<td>4291 (36)</td>
<td>785 (34)</td>
<td>399 (27)</td>
<td>347 (31)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>South</td>
<td>4227 (35)</td>
<td>1148 (50)</td>
<td>561 (38)</td>
<td>271 (24)</td>
<td></td>
</tr>
<tr>
<td>West</td>
<td>1912 (16)</td>
<td>152 (7)</td>
<td>506 (34)</td>
<td>412 (36)</td>
<td></td>
</tr>
<tr>
<td>Midwest</td>
<td>1535 (13)</td>
<td>213 (9)</td>
<td>18 (1)</td>
<td>101 (9)</td>
<td></td>
</tr>
<tr>
<td>Surgeon volume (no. of cases)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–9</td>
<td>3606 (44)</td>
<td>990 (52)</td>
<td>530 (55)</td>
<td>308 (53)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>10–29</td>
<td>2113 (26)</td>
<td>416 (22)</td>
<td>237 (25)</td>
<td>129 (22)</td>
<td></td>
</tr>
<tr>
<td>30–100</td>
<td>1884 (23)</td>
<td>450 (24)</td>
<td>189 (20)</td>
<td>130 (22)</td>
<td></td>
</tr>
<tr>
<td>&gt;100</td>
<td>553 (7)</td>
<td>34 (2)</td>
<td>13 (1)</td>
<td>16 (3)</td>
<td></td>
</tr>
<tr>
<td>Hospital location</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Urban</td>
<td>11,160 (93)</td>
<td>2242 (98)</td>
<td>1448 (98)</td>
<td>1083 (96)</td>
<td></td>
</tr>
<tr>
<td>Hospital teaching status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Teaching</td>
<td>6710 (56)</td>
<td>1548 (67)</td>
<td>752 (51)</td>
<td>627 (55)</td>
<td></td>
</tr>
</tbody>
</table>

This figure shows that a greater proportion of white patients are being treated by the highest-volume surgeons compared to non-white patients, a greater proportion of whom are being treated by lowest-volume surgeons.
mean total hospital costs ($5695). Differences in complication rates by racial group were not significant after adjustment in our multivariate model.

Race and Provider Volume Group Analysis

To understand the etiology of observed differences in patient outcomes by racial group and the relative contribution of access to care (as measured by surgeon volume group) versus other clinical and demographic patient differences, we performed a subgroup analysis for provider volume by race (Table 6). Differences in clinical and economic outcomes by race persisted even after adjusting for surgeon experience. For example, the mean total cost of thyroidectomy for blacks and Hispanics was higher compared with that for whites for all surgeon volume groups ($P < 0.01$), though it was least pronounced for the highest-volume surgeon group ($>100$ cases per year), where there was no statistically significant difference ($P = 0.059$).

LOS also was significantly longer for blacks and Hispanics compared with whites for all surgeon groups except the highest-volume group, where the differences were not statistically significant. Complication rates after thyroidectomy were not significantly different by race within surgeon volume groups; analysis was compromised by small cell sizes and the relative rarity of this outcome for highest-volume surgeons.

It appears that although patients of all racial groups are increasingly being referred away from lowest-volume thyroid surgeons to surgeons who perform more of these procedures, the discrepancy in access between races has only widened with time. We compared data from HCUP-NIS for 2003–2004 with similar data from 1999 to 2000. The proportion of thyroidectomies performed by low-volume surgeons fell across all race groups (Fig. 2A). The decline was greatest for whites (slope $-19.7$); it was smallest for blacks (slope $-3.5$).
The widening gap in access between races was most pronounced with regard to highest-volume surgeons (Fig. 2B). In 1999–2000, 1% of whites had thyroidectomy by this group; by 2003–2004, this had increased to 7% (slope 5.7). By comparison, blacks undergoing surgery by this highest-volume group rose from 0.2% to 1.8% (slope 1.6), and Hispanics showed even less increase, from 0% to 1.3% (slope 1.3).

**DISCUSSION**

This study is the first to examine the effects of race and ethnicity as predictors of outcomes from thyroidectomy. Compared with whites, blacks and Hispanics have longer length of stay (LOS), higher total hospital costs, and a trend toward higher complication rates after thyroid surgery. This finding was robust, in that differences in LOS and costs persisted even after adjusting for all other independent demographic and clinical predictors of outcome in the HCUP-NIS dataset. Blacks and Hispanics were more likely to undergo procedures by low-volume surgeons; interestingly, there were no highest-volume surgeons in the South. These findings lend credence to access limitations being a principal explanation for the observed discrepancy in outcomes by race.

High-volume surgeons performed a greater proportion of procedures on whites. Although the share of thyroid procedures performed by low-volume surgeons decreased over time, the rate of decline was greater among whites compared with blacks and Hispanics. High-volume surgeons increased their share of the total number of thyroid procedures for all races, but the rates of increase among blacks and Hispanics were significantly lower than for whites. Some of the observed differences in outcome could be the result of differences in stage of disease by race. With respect to benign thyroid disease, black patients had a significantly greater number of substernal goiters than whites, suggesting advanced disease progression. This finding was confirmed by an increased rate of urgent or emergent admission for thyroidectomy among blacks and Hispanics compared with whites. The suggestion of more advanced disease and the higher rates of urgent and emergent admissions may account for some of the longer LOS and higher costs in these racial groups.

Racial and ethnic disparities in health care outcomes have been well described in the literature. According to the National Center for Health Statistics, there were increases in observed life expectancy for whites and blacks between 2002 and 2003 (0.2 and 0.3 years, respectively). However, whites continue to have a significantly longer life expectancy than blacks (77.9 and 72.6 years, respectively). Elimination of these survival disparities is an essential component of the national agenda to improve the quality of health care. In 2001, the Institute of Medicine issued a landmark report on the need to revise the organization and delivery of health care in the United States. Specifically, the Committee on the Quality of Health Care in America set forth a statement of purpose, in which "equitable health care," one of 6 essential dimensions for quality of care, was defined as "care that does not vary in quality because of personal characteristics such as gender, ethnicity, geographic location, and socioeconomic status." Still, evidence is lacking to suggest that broad-scale change has been affected. Members of racial/ethnic minority groups continue to be at risk to receive less intensive and/or lower quality care for a variety of medical and surgical conditions. Sequist et al studied a population of patients receiving care for diabetes mellitus in a single multispecialty group and found significant racial disparities with respect to...

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Racial Groups N (%)</td>
<td>White</td>
<td>Black</td>
<td>Hispanic</td>
<td>Other</td>
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<tr>
<td>Mean total costs ($)</td>
<td>11,965 (70.9)</td>
<td>2298 (13.6)</td>
<td>1484 (8.8)</td>
<td>1131 (6.7)</td>
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<td>Volume groups</td>
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<td>6415 (0.001)</td>
<td>5910 (0.004)</td>
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<td>6453 (0.001)</td>
<td>4499 (0.001)</td>
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<td>5000 (0.001)</td>
<td>5854 (0.001)</td>
<td>3619 (0.001)</td>
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<td>9386 (0.001)</td>
<td>9032 (0.001)</td>
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<td>Volume groups</td>
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<tr>
<td>1–9</td>
<td>1.96 (0.001)</td>
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<td>Complications (%)</td>
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<tr>
<td>Volume groups</td>
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</tr>
<tr>
<td>1–9</td>
<td>4.9 (0.469)</td>
<td>5.8 (0.452)</td>
<td>4.0 (0.458)</td>
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<td>10–29</td>
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<td>30–100</td>
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<td>3.2 (0.458)</td>
<td>3.1 (0.458)</td>
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<tr>
<td>&gt;100</td>
<td>2.9 (0.05)</td>
<td>— (0.05)</td>
<td>15.4 (0.05)</td>
<td>— (0.05)</td>
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</tbody>
</table>

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late-survival probability at both 1 and 5 years (white patients, Gray et al found that blacks have a decreased bypass surgery in a population of medically insured black and respective.

towards significance for 5 and 9 of the 10 procedures, (therefore) sphincter-preserving operations (P = 0.019).10 These findings were robust, in that the findings persisted even after adjustment for nodal status, tumor size, and stage of disease. Though the implications for overall survival are not clear, the authors hypothesize that Hispanics have both decreased access to care and a lower quality of care overall.

In the National Cancer Institute’s 1994 Black/White Cancer Survival Study, black women with breast cancer appeared to have higher all-cause and disease-specific mortality rates, after adjustment for breast cancer stage, treatment, comorbidities, pathologic, and sociodemographic variables.29 Although the authors attributed this to sociodemographic variables, similar epidemiologic observations have led others to postulate that cancer biology in blacks and whites is fundamentally different, with this difference accounting for observed disparities in patient outcomes. Bach et al examined this theory via a meta-analysis of 54 studies measuring overall survival for black and white patients who underwent treatment for all cancers, excluding malignant melanoma, pediatric tumors, malignancies in patients with human immunodeficiency virus, and premalignant conditions, such as polyps of the colon. There was an increased risk of disease-specific mortality for blacks, even when corrected for deaths due to other causes.30 The authors concluded that disparities in cancer outcomes by race were more likely due to differences in stage of disease at presentation, method of treatment, and mortality from comorbid conditions.

A 10-year review of 14,291 patients with colon cancer who underwent surgery in Maryland examined the potential association of prehospital factors with short-term patient outcomes such as bowel obstruction, hemorrhage, perforation, and in-hospital mortality.6 Ahuja et al postulated that racial disparities can lead to a delay in diagnosis and more advanced cancer stage at the time of presentation. In multivariate analyses, blacks were more likely to have life-threatening symptoms at presentation, independent of socioeconomic status (P = 0.001). They also had higher in-hospital mortality rates compared with whites in all socioeconomic groups (P = 0.015). This was especially true for the higher socioeconomic groups (P = 0.001).6 Martinez et al have shown disparities in outcome among Hispanic patients with colorectal cancers. The Surveillance, Epidemiology and End Results database was used to compare rates of neoadjuvant therapy and sphincter-preserving surgery between Hispanics and non-Hispanic whites with rectal cancer. Non-Hispanic whites were more likely to have neoadjuvant therapy (P < 0.001) and (therefore) sphincter-preserving operations (P = 0.019).10 These findings were robust, in that the findings persisted even after adjustment for nodal status, tumor size, and stage of disease. Though the implications for overall survival are not clear, the authors hypothesize that Hispanics have both decreased access to care and a lower quality of care overall.

Numerous studies have documented the association between referral to high-volume centers and patient outcomes, particularly for cardiovascular and oncologic surgical procedures; significantly reduced perioperative mortality rates are seen in patients referred to high-volume centers.22–25 Liu et al found a substantial racial and ethnic disparity in the characteristics of patients receiving care at high-volume hospitals in California between 2000 and 2004 for a subset of 10 cardiovascular, oncologic, and orthopedic inpatient surgical procedures.28 Blacks were less likely than whites to receive care at high-volume hospitals for 6 of the 10 procedures (P < 0.05), whereas the rates for Asians and Hispanics trended towards significance for 5 and 9 of the 10 procedures, respectively.

“Equitable health care,” as defined by the 2001 Institute of Medicine report, appears to be dependent on a number of biologic, cultural, and socioeconomic factors. Demographic and personal characteristics include gender, geographic location, and socioeconomic status, including income and education. Even when controlling for these traits, however, racial and ethnic disparities in outcomes persist. Although inequality in access to health care accounts for a portion of outcome disparities by race, there are likely other nonmedical determinants of health, such as a person’s social environment and cultural beliefs, which might be contributing factors, as well.21

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FIGURE 2. A, Low-volume (1–9) surgeon share of thyroid procedures, by race over time. The proportion of thyroidectomies performed by low-volume surgeons is decreasing across all race groups; however, the decline is greatest for whites and smallest for blacks. B, Highest-volume (>100 cases) surgeon share of thyroid procedures, by race over time. There is an increasingly widening gap in access to the highest-volume surgeons between white and non-white patients.
Cultural differences also have been shown to play a role in outcome disparities. They can be broken down into patient and provider factors. From the patient perspective, these differences include: patient preference; cultural beliefs resulting in mistrust of health care providers and/or the health care system; and language barriers between patients and their health care providers. From the perspective of physicians, these include potential racial and ethnic biases and lack of cultural competency; studies have shown that cultural competency is critical in bridging cross-cultural gaps between patients and providers, which can be created by a (mutual) lack of cultural understanding, different paradigms for illness, and health illiteracy. Although these biases may exist below the level of conscious awareness, they nevertheless might perpetuate racial and ethnic disparities in health care outcomes.

On the basis of HCUP data, patients with benign and malignant diseases of the thyroid have a trend towards significantly fewer complications after thyroidectomy when they have access to high-volume surgeons (Table 5). Sosa et al demonstrated this finding with a cross-sectional analysis of all patients undergoing thyroidectomy in Maryland between 1991 and 1996. Patients who received care from the highest-volume surgeons (>100 cases per year) had significantly shorter LOS and lower complication rates. One component of the disparity seen in thyroidectomy outcomes may be due to a difference in access to care, ie, high-volume providers.

There are limitations to our study, including those inherent to use of a large administrative database. Though HCUP-NIS is widely used in health services research, it is only a 20% sample of US hospitals and does not include federal hospitals. Adjustment was made for patient comorbidity using the HCUP ALRDRG-3M, which might have been incomplete. We relied on ICD-9 procedure and diagnosis codes to extract cases; ICD-9 reporting and coding errors could lead to different results, although this has not been shown to be a pervasive problem for HCUP data. In addition, we were unable to thoroughly adjust for extent of thyroid disease, particularly with respect to stage of thyroid cancer. Our multivariate analyses encompassed all socioeconomic variables in HCUP, including median income, primary payer, and rural versus urban location. Other known social gradients, which could affect outcomes and access to high-volume surgeons, such as patient education, occupation, and wealth, are unavailable in the dataset.

The reasons for racial and ethnic disparities are intricate; we sought only to document potential disparities in thyroidectomy outcomes among different races. Even for thyroidectomy, a surgical procedure that is common and generally considered to be safe with a low risk of morbidity and mortality, there are significant racial and ethnic disparities in outcomes. Furthermore, our findings suggest that these disparities are pervasive and perhaps worsening, in that there is a widening gap in access to high-volume thyroid surgeons among different races. This is only an initial study of thyroidectomy outcomes based on race and ethnicity. More data are needed to clarify the significance of the association between race and ethnicity and outcomes in endocrine surgery and to direct possible interventions to narrow this apparent gap.

REFERENCES

15. 3M Health Information Systems. All-Patient Refined Diagnosis Related Groups (APR-DRGs) Methodology Overview TMHIS. Wallingford, CT: 3M Health Information Systems; 1998.
The Optimal Timing of Intestinal Transplantation for Children With Intestinal Failure

A Markov Analysis

Steven R. Lopushinsky, MD, MSc,*† Robert A. Fowler, MD, MSc,† Girish S. Kulkarni, MD,*† Annie H. Fecteau, MD, MSc,*‡ David R. Grant, MD,* and Paul W. Wales, MD, MSc*†‡

Objective: Identify an optimal approach to the timing of intestinal transplantation for children dependent on total parenteral nutrition (PN).

Summary Background Data: Children with short bowel syndrome are frequently dependent on PN for growth and development. Intestinal transplantation is often considered after PN-related complications occur, but optimal timing of transplantation is controversial.

Methods: A Markov analytic model was used to determine life expectancy (LY) and quality-adjusted life years on a theoretical cohort of 4-year-old subjects for two treatment strategies: (1) standard care consisting of PN and referral to transplantation according to accepted guidelines and (2) early listing for isolated small intestine transplantation.

Results: Early listing for intestinal transplantation was associated with 0.27 additional life years (13.16 vs. 12.89) and 0.76 additional quality-adjusted life years (10.51 vs. 9.75) as compared with current standard care. The unadjusted analysis was sensitive to the development of PN-associated liver disease, at a threshold of approximately 11% per year, and its related probability of dying at a threshold of 80% 2-year mortality. Early listing for transplantation was the dominant strategy until the probability of late bowel rejection reached 35% per year.

Conclusions: Children with short bowel syndrome dependent on PN should be considered for intestinal transplantation earlier than what is current practice.

The early experience of small bowel transplantation was laden with high rates of graft failure and mortality.1,2 Recent advances in immunologic suppression have made intestinal transplantation a more attractive therapeutic option in patients with intestinal failure. Many transplantation programs now achieve 1-year graft and patient survival rates in excess of 80%.1,3–7

The introduction of total parenteral nutrition (PN) programs in the 1970s revolutionized the prognosis of children with short bowel syndrome.8 Although many children will eventually achieve nutritional autonomy by way of intestinal adaptation, up to 20% to 40% of children with short bowel syndrome remain PN-dependent.9,10 Children with short gut are usually considered for transplantation after the development of complications on PN,9 including blood stream infection, sepsis, and liver dysfunction.8,10–13 At present, quality of life is not accepted as an indication for intestinal transplantation.8,14 There are no clinical trials or cohort studies that explicitly compare survival or quality-adjusted survival in children treated with standard care versus early listing for transplantation. In the absence of such data, decision-analytic techniques can model complex clinical problems such as timing of transplantation.

MATERIALS AND METHODS

Reference Case Definition

This study considered the base case of a 4-year-old male child with acquired short bowel syndrome dependent on PN in excess of 2 years. Because intestinal adaptation may evolve over 1 to 2 years11 and few patients beyond 3 years of age will wean completely from PN,15 we made the assumption that this child would not undergo any further intestinal adaptation. Primary outcomes were life expectancy (LY-years) and quality-adjusted life years (QALYs). Secondary outcomes included LYs and QALYs over a 5-year time horizon. We chose a societal perspective to capture all-important clinical outcomes in patients with short bowel syndrome.

Decision Model

A multistate Markov analytic model was created (Tree-Age Pro 2005, Williamstown, MA) to evaluate the survival and quality-adjusted survival of 2 strategies: (1) usual care...
(delayed transplantation pending PN-complication), or (2) early listing for isolated small bowel (ISB) transplantation (Fig. 1A). Time was represented using 1-month cycle in which patients could move among health states according to varying probabilities of morbidity and mortality until a lifetime horizon was reached. Mortality rates were based upon Canadian life tables, adjusted for disease-related mortality.16 The transition among health states in both the standard care and early listing arms is represented by a simplified Markov health state diagram in Figure 1B. In this model, patients receiving standard care were maintained on PN throughout their lifetime, until the patient died of disease related or unrelated causes, or an indication for intestine transplantation was met, specifically: (1) at least 2 intravenous line related-sepsis events, (2) the thrombosis of at least 3 central veins, or (3) the development of liver dysfunction.9 At the time of listing, all patients were directed to an ISB graft, except in the setting of liver disease in which case they were listed for combined intestine-liver grafting.

The outcomes of transplantation, including its potential complications, apply to all patients undergoing the procedure, either early or late. In the early postoperative period (<90 days), patients may develop major operative complications (eg, anastomotic leak or hemorrhage requiring reexploration) or early technical graft failure. Subsequent complications of transplantation and immunologic suppression included rejection, sepsis, and posttransplantation lymphoproliferative disorder (PTLD). Among surviving patients, the degree of nutritional independence was classified as PN-dependent or PN-independent.

**Data Sources, Probabilities, and Utilities**

A comprehensive review of the English-language literature was performed to determine the probabilities for each of the branches in the tree. Relevant articles were found through a Medline search using the terms “Small Intestine” and “Transplant” or “Transplantation.” Where possible, probabilities relating to small intestine transplantation are derived from the International Intestine Transplant registry.1,17 PN literature was searched using the terms “Short Bowel Syndrome” and “Total Parenteral Nutrition” or “Home Parenteral Nutrition” or “Parenteral Nutrition.” Bibliographies of articles, abstracts and conference proceedings, and personal files were also searched for additional relevant information. Publications were evaluated for best evidence and where possible, data were restricted from 1999 onward given the evolution in transplantation care.1 Monthly transition state probabilities represent the likelihood of developing a given outcome or moving to a new health state. Where available, 30-day transition state probabilities were converted from data expressed as rates. Otherwise, we assumed an exponential distribution for the cumulative risk and solved for its monthly probability. Data from multiple case-series were weighted by their respective number of patients to estimate the transition probability used for modeling.

**Total Parenteral Nutrition**

The most common side effect on PN is catheter-related bloodstream infections and sepsis, accounting for approximately one-half of rehospitalizations in this patient population.15 The incidence of sepsis during PN ranges between 1 and 4 infections per 1000 PN days.16 Rates of catheter infections among hospitalized patients tend to be higher; 8.4 episodes per 1000 patient-days in 1 study.19 A baseline value of 1.6 infections per 1000 PN days (monthly probability of 0.047) was chosen as it is derived from the largest clinical pediatric series reported.10 It was assumed that the mean hospital stay for each sepsis admission was 15 days and that approximately 4% of patients die as a result of the infection.19
The incidence of catheter-related central-vein thrombosis is approximately 0.2 episodes per 1000 catheter days.\textsuperscript{20} Liver dysfunction is expected to eventually develop in approximately 40% to 60% of pediatric patients on PN (Annual risk approximately 10%–17%).\textsuperscript{10,21} In an adult study of PN patients, the median time to death after an initial increase in serum bilirubin was 10.8 months,\textsuperscript{22} and our models reflect this reduced life expectancy.

**Waiting List**

Monthly probabilities of transplantation were provided by the Universal Network for Organ Sharing for children up to the age of 5 years (based on data as of January 6, 2006).

**Small Intestine Transplantation**

Early complications were defined as those occurring within 90 days of surgery. We estimated that 1% of rejection episodes would result directly in patient death and 10% would result in graft failure. Given the higher levels of immunosuppression required to treat rejection episodes, post-rejection infectious complications were set equal to those in the perioperative period.

Definitions of infectious-related complications varied significantly across the literature resulting in a wide range of estimates. Among infectious complications, it was estimated that approximately 6% would result in patient death and on average require 15 days of hospitalization, although this was varied in sensitivity analyses according to the range of published rates.\textsuperscript{3,7,23–25}

Patients who develop PTLD could die (monthly base probability 0.02), recover (monthly base probability 0.50), or continue within the PTLD state.\textsuperscript{1,3,24,26} Because treatment of PTLD involves the reduction in immunosuppression, the immediate rate of rejection was set equivalent to that of early postoperative rejection.

**Utilities**

Utilities are a quantitative measure of patient preference for a given health state. We are not aware of any study

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**TABLE 1. Monthly Transition State Probabilities and Health State Utilities**

<table>
<thead>
<tr>
<th>Item</th>
<th>Monthly Probability Estimate</th>
<th>Plausible Range</th>
<th>References</th>
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</thead>
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<tr>
<td><strong>PN</strong></td>
<td></td>
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<tr>
<td>Line sepsis</td>
<td>0.0475</td>
<td>0.03–0.226</td>
<td>10,19</td>
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<tr>
<td>Sepsis death</td>
<td>0.037</td>
<td>0.014–0.18</td>
<td>19,38–40</td>
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<td>Lose vascular access</td>
<td>0.0063</td>
<td>0.0047–0.0079</td>
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<tr>
<td>Liver complications</td>
<td>0.0115</td>
<td>0.0085–0.0152</td>
<td>9, 10, 21, 41</td>
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<tr>
<td>Death due to liver complication</td>
<td>0.0884</td>
<td>0.0649–0.319</td>
<td>22, 41</td>
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<td><strong>Wait list</strong></td>
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<tr>
<td>Probability of ISB transplant</td>
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<td>0.0539–0.143</td>
<td>UNOS personal communication</td>
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<tr>
<td>Probability of ILT transplant</td>
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<td>0.0631–0.140</td>
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<td><strong>Posttransplant</strong></td>
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<td>Technical failure</td>
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<td>0.0–0.05</td>
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<td>Rejection (late)</td>
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<td>Infection (early)</td>
<td>0.639</td>
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<td>Infection (late)</td>
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<td>Infection-related death</td>
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<td>PTLD</td>
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<td>0.0017–0.0216</td>
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<td>0.0191</td>
<td>0.0143–0.0238</td>
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<td>Independence from PN</td>
<td>0.625</td>
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<td><strong>Utilities</strong></td>
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<td>PN-dependent</td>
<td>0.61</td>
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<td>Peri-transplant (0–3 mo)</td>
<td>0.6</td>
<td>0.5–0.86</td>
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<td>Posttransplant well (PN-independent)</td>
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<td>Liver dysfunction</td>
<td>0.2</td>
<td>0.15–0.3</td>
<td>36, 48, 49, 54–57</td>
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</table>

Probabilities of death due to a complication are dependent on first developing the complication (ie, sepsis, rejection, and PTLD).
that specifically describes the utilities of children either for PN or for intestinal transplantation. Richards and colleagues, however, found younger adults to have a higher utility than older adults while on PN.\(^\text{28}\) A cost-utility analysis of home PN in Toronto, Ontario determined a utility of 0.7 based on measurements from 37 patients,\(^\text{29}\) but later acknowledged that this value was unexpectedly high.\(^\text{30}\) Quality of life in adult patients on home PN has been shown to be similar to that of chronic renal failure patients on dialysis.\(^\text{31}\) Utilities for end-stage renal disease were therefore used to form a broad reference range for the utility of PN in our sensitivity analysis.\(^\text{32}\) In the pediatric population with chronic illness, utilities have ranged from 0.61 to 0.89 for mild to severe disability.\(^\text{33}\)

Pediatric intestine transplant recipients with functional grafts report similar quality of life scores to normal school children.\(^\text{34}\) Utilities for liver transplantation were used as proxy measures to estimate health status after intestine transplantation.\(^\text{35-37}\) In a cross-sectional survey of children surviving liver transplantation at least 2 years, the mean utility measured was 0.86.\(^\text{37}\) Because many children remain on PN for long periods after intestinal transplantation, lower utility values were applied to reflect ongoing nutritional dependence. Additional disutilities were applied to episodes of sepsis, perioperative complications, rejection, and liver dysfunction. Selected utilities are summarized in Table 1.

**Sensitivity and Threshold Analyses**

Sensitivity analysis is a method to test uncertainty in the hypothetical model. One-way sensitivity analyses were performed by repeating the LY and QALY analyses over the respective range of values for all model variables and utilities. Threshold values were determined for each variable beyond which the optimal strategy changed. Variables were considered sensitive if a threshold value occurred within a predetermined plausible range of values. The range in values represents the broadest values identified in the literature or where unavailable ±25% of the chosen probability value. Two-way and three-way sensitivity analyses were also performed but did not change the interpretation of the results and therefore are not reported.

**Base Case Analysis**

Early listing for isolated intestinal transplantation resulted in a greater life expectancy (13.16 years) than that of standard care (12.89 years), a gain of 3.2 months (Table 2). Early listing also resulted in an incremental gain of 9.1 quality-adjusted life months (Early listing, 10.51 QALY; Standard care, 9.75 QALY).

A prespecified secondary analysis was performed with a 5-year time horizon given the relatively early experience of modern transplantation. Similar to the primary analysis, early listing was the dominant strategy, with respect to quality-adjusted survival, 2.96 QALY versus 2.66 QALY for early listing and usual care, respectively. Unlike the primary analysis, however, unadjusted survival favored the delayed transplantation strategy with expected life-year values of 4.14 and 3.95, respectively.

**Model Validation**

One-year survival for early listing and usual care was 88% and 94%, respectively. Two-year, 5-year, and 10-year survival for early listing and usual care were 79%/86%, 64%/64%, and 46%/44%, respectively (Fig. 2 survival curves). Modeled survival closely resembles transplant registry outcomes after 1998.\(^\text{1}\) The North American Home Parenteral and Enteral Nutrition Patient Registry reports 1-year and 4-year survival rates of 94% and 80%, respectively.\(^\text{9}\) The slightly higher long-term survival in the PN registries compared with the model is an expected finding as unlike the clinical databases, our cohort is restricted to those patients who will not undergo further intestinal adaptation.

**Sensitivity Analyses**

Life expectancy was most sensitive to the occurrence of PN-liver disease (Fig. 3) and late graft rejection. When the monthly probability of developing liver complications while on PN is <1% (annual baseline risk approximately 11%), life-expectancy analysis favors a delayed listing treatment strategy. After the onset of liver disease, if the annual probability of dying is less than approximately 56%, delayed listing for transplantation is favored. Early transplantation was favored up to a 35% annual risk of late rejection. Other variables were sensitive within the model, yet only at the margins of their respective ranges (Table 3). For example, of the posttransplantation parameters early infection

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### Table 2. Base Case Results

<table>
<thead>
<tr>
<th>Treatment Strategy</th>
<th>Life Expectancy (yr)</th>
<th>Quality-Adjusted Life Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early transplant listing</td>
<td>13.16</td>
<td>10.51</td>
</tr>
<tr>
<td>Standard care</td>
<td>12.89</td>
<td>9.75</td>
</tr>
<tr>
<td>Incremental gain</td>
<td>0.27</td>
<td>0.76</td>
</tr>
</tbody>
</table>

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**FIGURE 2.** Survival curves by treatment strategy.
and infectious-related mortality rates (threshold = 93% per month), were sensitive on one-way analysis.

In the adjusted analysis, the model was sensitive only to the probability of dying from an episode of sepsis after transplantation. Delayed transplantation was the preferred strategy only if the rate of mortality associated with sepsis in the posttransplant patient remained less than 9.4%. Early transplantation provided increased quality-adjusted life expectancy throughout all other sensitivity analyses, including those performed on the respective health state utilities.

**Interpretation**

The decision to list a pediatric patient for intestinal transplantation is complex. This is the first decision model to help guide clinicians and patients in the optimal timing of transplantation. We have demonstrated that early listing for ISB grafting is favorable over a strategy of long-term PN. The major driver of this finding is the accumulated risk of PN complications, particularly the risk of bloodstream infections and PN-associated liver disease, over the patient’s life expectancy. Sensitivity analyses indicated that delayed listing is only preferable when the incidence of PN-associated liver disease is less than 11% per year, which is much lower than currently observed. Also, consistent with clinical observation, we found that rejection rates were an important determinant of graft and patient survival. In our model, early listing for transplantation is indicated as long as rejection rates beyond the perioperative period were below 35% annually, a benchmark attained by most transplantation programs.

For early transplantation to be considered as an alternative to PN, it should have an equivalent or improved mortality rate, improved quality of life, and have an acceptable economic comparison with the current standard of care. High volume centers now report 1-year patient survival rates in excess of 85% to 90%. Accordingly, it is generally accepted that transplantation is indicated when life-threatening PN-related complications develop. At what point however should indications for transplant broaden to include uncomplicated patients or those burdened by poor quality of life? In this study, having adjusted for quality of life, early transplantation was the preferred strategy even while considering broad ranges of clinical variables and utilities. Several other studies have examined quality of life while receiving home PN, and after intestinal transplantation, but few incorporate both therapies. Two small adult studies reported similar or improved quality of life after transplantation in comparison to pretransplant PN. Jeppesen et al reported that quality of life was reduced in short bowel patients requiring PN compared with those not receiving PN, and was similar to patients requiring dialysis for chronic renal failure. Children remote from intestinal transplantation perceive their quality of life similar to that of other school children. After transplantation, 80% to 95% of children become independent of PN, grow normally and attend school.

![FIGURE 3. Selected one-way sensitivity analyses. Threshold value: Probability below which the usual care strategy is preferred. If the probability of developing liver disease while on PN is below approximately 1% per month (approximately 11% per year), then the usual care strategy is favored. When the probability of liver disease exceeds this value, the early listing strategy is favored. The model is also sensitive to the monthly probability of dying from liver disease after PN-liver complications develop. For monthly probabilities of death less than approximately 7% (approximately 60% per year), the usual care strategy is favored, otherwise the early listing strategy is favored.]

(threshold = 93% per month) and infectious-related mortality rates (threshold = 10.0% per month), were sensitive on one-way analysis.

In the adjusted analysis, the model was sensitive only to the probability of dying from an episode of sepsis after transplantation. Delayed transplantation was the preferred strategy only if the rate of mortality associated with sepsis in the posttransplant patient remained less than 9.4%. Early transplantation provided increased quality-adjusted life expectancy throughout all other sensitivity analyses, including those performed on the respective health state utilities.
There are several important limitations to acknowledge in our study. Caution should be taken in interpreting our long-term results over a lifetime time horizon given the paucity of long-term intestine transplant data in the literature. This is simply a function of the relatively few procedures that have been performed in the modern era of transplantation. Most of the observed survival gains seen recently have been at the 1- to 2-year mark. Although improvements in outcome may develop for both long-term PN and posttransplantation survival, the gains in posttransplantation survival have occurred at a much more rapid pace, and it is reasonable to expect continued improvements over the next period of intestinal transplantation evolution. More extensive data on the timing and incidence of posttransplant complications is crucial for future research and clinical decision making. Data collection for the Intestine Transplant Registry data may need to be altered to capture this information. Second, there is a lack of formal studies determining the utility of small intestine transplant health states in either the adult or pediatric populations. Irrespective, the quality-adjusted analysis was robust to broad values of utilities for all health transition states. Third, decision models cannot capture the full variability in clinical practice, nor the full range of characteristics of individual patients. The Markov model assumes that health states are mutually exclusive and lack memory from previous experience. In reality, the timing and propensity to list a patient may be dependent on physician enthusiasm, patient preference, and institutional practice patterns. Fourth, the base case in this study was a 4-year child, which likely does not represent the majority of children who are listed for intestinal transplantation. We do not feel that this is a major limitation of the study however because we were interested from the outset in capturing a patient population where further intestinal adaptation is unlikely. The results of this study should be generalizable to any pediatric patient where the probability of sufficient intestinal adaptation is remote. Finally, our model does not examine cost differences in early or delayed listing strategies. The economic implications of the strategies compared in our model are unclear. There is literature to suggest that successful transplantation is cost-effective 1- to 2-years after transplantation but no formal economic analysis has been completed.

In the absence of a randomized controlled trial, we provide evidence that may justify earlier listing of stable PN-dependent patients for intestinal transplantation than what is currently practiced. Although the demonstrated survival advantage of intestinal transplantation is small, it more importantly reflects relative clinical equipoise in the 2 therapies. Quality of life should now be included in the discussion when considering transplantation.

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The Michigan Surgical Quality Collaborative
Will a Statewide Quality Improvement Initiative Pay for Itself?

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Objective: In this article, we detail a unique collaboration between hospitals in Michigan and a major third party payer, using a “pay for participation model.” The payer has made a significant investment in this regional surgical quality improvement (QI) program and funds each center’s participation.

Results: Based on the documented costs and incidence of surgical complications at our center, we estimate that a 1.8% annual reduction in complication rates is required for the payer to recoup its investment in this regional QI program. If we achieve our goal of a 3% reduction in complications per year over the 3-year program, the payer will save $2.5 million in payments. Our findings suggest that only a very modest improvement in surgical results, of a magnitude that seems realistically achievable based on similar QI initiatives, is necessary to financially justify payer involvement in a statewide quality improvement initiative.

Conclusion: The framework of this program should be used by surgeons to attract private payers into QI collaboratives, facilitating improved patient outcomes and decreased health care expenditures.


We have previously reported that surgical complications are expensive, and that payers, rather than providers, bear the financial burden associated with complications and poor surgical outcomes.1–4 These findings provide a rationale for active partnerships among payers, hospitals, and surgeons in efforts to systematically assess and improve surgical care processes and their resultant outcomes. Although it is the patient who is the most obvious beneficiary of organized, data-driven, multi-institutional quality improvement initiatives, we were interested in what level of improvement in surgical quality would be necessary for payers to recoup their costs in supporting such quality improvement efforts. Our findings suggest that only a very modest improvement in surgical results, of a magnitude that seems realistically achievable based on similar quality improvement (QI) initiatives, is necessary to financially justify payer involvement in a statewide quality improvement initiative.

Blue Cross and Blue Shield of Michigan and Blue Care Network (BCBSM/BCN) and surgical leaders within the state of Michigan have entered into a unique “pay for participation” quality improvement program, the Michigan Surgical Quality Collaborative (MSQC). This partnership is 1 of 6 such “Value Partnerships” supported by BCBSM. The MSQC uses the American College of Surgeons—National Surgical Quality Improvement Program (ACS-NSQIP) as its reporting infrastructure. In this partnership, BCBSM/BCN underwrites the costs associated with most, or, more recently, all of the hospital data collection costs. In addition, BCBSM/BCN supports the costs of the Coordinating Center, which is responsible for convening collaborative providers, disseminating regional process, and outcomes reports, working with the ACS to assure data completeness and accuracy, and orchestrating statewide quality improvement interventions. In return, hospitals agree to anonymously share ACS-NSQIP data on a statewide basis, assure such data are complete and accurate, actively participate in consortium quality assessment and improvement activities, and harness the learning achieved to internal quality improvement efforts. In this way, problems unique to the state of Michigan can be identified and appropriate statewide quality improvement initiatives can be formulated and catalyzed. In this article, we report the creation of the MSQC and review the financial justification for its existence.

CREATION OF THE MSQC

The MSQC was designed as a partnership among the ACS, various Michigan hospitals, and BCBSM/BCN. The purpose of the partnership is to advance surgical quality in Michigan, by using the data feedback and QI initiatives based on the ACS-NSQIP, with the financial support of a major third party payer in our state, BCBSM/BCN. We prepared a “business case for quality” by documenting that surgical complications, as defined by ACS-NSQIP, are expensive, and that the payer bears the largest share of additional expense associated with complications.1–3 These arguments were critical in interesting BCBSM/BCN to fund this broad-ranging surgical QI initiative.
The MSQC is based, in part, on the assumption that collaborative, multi-institutional, regional implementation of a national QI initiative (ACS-NSQIP) could be particularly effective in improving surgical quality. Working together in a region, collegial relations can be easily developed when the numbers of hospitals involved is relatively small, and key individuals know each other. These relationships can serve as the foundation for interinstitutional sharing about what works in surgical practice. This approach takes participants beyond the more passive approach used when individual hospitals rely on national quality reports to independently guide internal quality improvement efforts. Site visits to determine “best practices” are more feasible locally, and an auditing function, already present in the ACS-NSQIP, is more easily enhanced by a local reviewer. Previous reports have documented the effectiveness of regional QI initiatives within the State of Michigan.2-9

Two factors figured prominently in the decision by Michigan hospitals to participate in the MSQC partnership. First, a fundamental tenet was established that BCBSM/BCN would not have knowledge of risk-adjusted outcomes of any specific hospital. This information resides at the administrative center of the MSQC at the University of Michigan rather than BCBSM/BCN. Thus, BCBSM/BCN would not use hospital or surgeon-specific data for making judgments or determining payment. Data would be solely for quality improvement purposes. The second most important factor was the degree to which BCBSM/BCN was willing to offset the hospital costs for participation in ACS-NSQIP. Three Michigan hospitals enrolled in ACS-NSQIP before any BCBSM funding was available, whereas 12 additional hospitals enrolled in ACS-NSQIP more recently, when approximately 80% of costs were covered by BCBSM. A more recent expansion of this support as part of BCBSM’s hospital incentive program will more than cover all costs for MSQC participant hospitals and in many cases provides substantial additional funds as a catalyst and reward for such participation. Twenty-seven additional hospitals have showed interest in response to this new incentive program.

**PARTICIPATION OF THE THIRD PARTY PAYER**

A financial benefit was not the most important motivation for BCBSM/BCN in entering into the MSQC partnership. Third party payers wish to provide quality care at the best value for their subscribers. Also, the third party payer is interested in demonstrating value for its major purchasers, which in the state of Michigan includes large national manufacturers such as General Motors Corporation, Ford Motor Company, and Daimler-Chrysler Corporation. BCBSM/BCN, by virtue of its large market share, is expected to influence change in the medical environment. However, the best strategy to achieve this end has been unclear.

Other initiatives have not been instrumental in catalyzing quality improvement in surgical practice in Michigan. A policy of “steering” patients to high-volume hospitals (the Leap Frog initiative) was seen by BCBSM/BCN as not practical; it controls such a large market share (47%) that its patients would quickly overwhelm the capacity of a few qualifying, high-volume hospitals. Instead, BCBSM/BCN favored a strategy which promoted and recognized improvements in quality at each individual hospital. This strategy, part of BCBSM’s Value Partnership program, and called by some pay for participation, rewards each hospital equally for participation in a statewide quality effort. This approach fosters participation in quality efforts, active collaboration across hospitals and surgeons with an explicit attempt to encourage sharing of knowledge and experience about what works and what doesn’t in quality improvement. In addition, pay for participation avoids the competitiveness of “pay for performance” schemes, which produce clear winners and losers.

BCBSM/BCN was motivated to join the MSQC partnership because the MSQC provides an optimal platform for improvement at each hospital. Because the ACS-NSQIP data definitions are standardized and the performance reports are risk adjusted, each hospital knows where it stands in the continuum of surgical quality in Michigan. “Best performers” can be easily identified, and best practices defined. When best practice information is distributed and systematically implemented in each hospital, the assumption is that quality will improve. A collegial atmosphere among participating hospitals is fostered because each hospital receives the same support from BCBSM/BCN for participation, and within the collaborative hospitals and surgeons are encouraged, but not required, to contribute expertise and seek it from peers.

**THE FINANCIAL JUSTIFICATION FOR A VALUE PARTNERSHIP**

In Figure 1, we describe the financial considerations we believe apply to the MSQC, particularly from the payer perspective. We have extrapolated these figures from our experience at the University of Michigan involving NSQIP cases and our TSI cost accounting system.2,3 With this assumption in mind, our model for predicting the level of improvement in outcomes required to break even and save money is as follows: 15 Michigan hospitals participate with an average general and vascular surgery volume of 3500 cases per year. A 3-year program would involve 157,500 cases. If we estimate a 14% complication rate and a cost per complication of $8287 to the payer, the cost of complications in this cohort is $182,700,000.2 Considering that BCBSM has a 47% market share, the overall cost of complications to BCBSM would be $85,900,000. If in the first 3 years of the program BCBSM/BCN supported 80% of the costs of data collection and all of the Coordinating Center costs, the sum of these costs would total approximately $5,300,000. If the MSQC can equal the 3% per year reduction in surgical complications that was achieved by the ACS-NSQIP-Patient Safety in Surgery Study, then BCBSM/BCN would make $2,500,000 on the program. The MSQC only needs to achieve a reduction in complications of 1.8% per year over the 3-year study period for BCBSM/BCN to financially break even on its investment. If these improvements in surgical quality could be maintained, the program would be either self-sustaining or profitable for BCBSM/BCN indefinitely.
A reduction of 1.8% or greater in the incidence of complications is likely obtainable, based on other experience with the implementation of NSQIP. In the application of NSQIP within the Veterans Administration, complications were reduced by 45% over a 10-year interval after implementation of the system.11,12 Most of the improvements were seen in the first 3 years of experience, but importantly this improvement was sustainable during the subsequent 7 years. It could be argued that the improvement was on the basis of widespread change in medical practice nationally, rather than a specific effect of NSQIP implementation. Without an appropriate control group with the Veterans Affairs (VA) system, there is no definitive way to address this criticism. However, a non-VA experience, the Patient Safety in Surgery trial, involving 14 large academic medical centers, recently demonstrated a 9% reduction in the incidence of complications over a 3-year interval, or 3% per year (Khuri, unpublished data, 2007). This trial involved only feedback of risk-adjusted data and no specific QI intervention, which is a more limited approach than has been taken by MSQC. Thus, the 3% annual reduction rate which we used as a benchmark in our calculations may represent a conservative estimate for improvement within the MSQC initiative.

**CONCLUSIONS**

In this article, we report the details of the creation of a unique collaboration between hospitals in a defined region and a major third party payer, aimed at recording surgical complications and identifying common practices to prevent future sources of postoperative morbidity across participating institutions. The MSQC was created on the foundation of the ACS-NSQIP, which has demonstrated the ability to realize significant and durable improvement in surgical outcomes among its participating hospitals. Based on these notable results and their associated financial implications, we have created a business case to justify the involvement of BCBSM in the administration of the MSQC QI initiative. The involvement of BCBSM and the application of their financial resources have in turn attracted additional participating institutions to the MSQC. There are 2 important limitations of our financial analysis used to justify the involvement of BCBSM. First, the financial data was generated at our single center, which is a large academic medical center, and our calculations may not apply to other hospitals in Michigan, most of which are community-based hospitals. Second, we have estimated the costs of the program to BCBSM/BCN based on the approximate $135,000 per year costs for an institution to participate in the ACS-NSQIP. This amount closely approximates the amount of data collection costs born by the health plan. However, hospitals can earn a varying amount of additional incentive payment for participation in a total of 6 such collaborative quality initiatives. The amount varies depending on the amount of total BCBSM/BCN payments to the hospital, which depend, in turn, on hospital volume and the proportion of patients at the hospital which are BCBSM/BCN members. This new incentive program went into effect in 2007, so we don’t know the precise costs of the program to BCBSM/BCN. Despite these limitations, we are confident that the MSQC will be a sound financial investment for BCBSM/BCN.

When an active QI intervention is added to the feedback of data via risk adjusted, comparative performance reports rather remarkable improvements in quality have been noted.7,9 Two QI interventions in Michigan, both supported, in part, by BCBSM/BCN, bear special mention. In the first, involving percutaneous coronary intervention, a collaborative of Michigan hospitals was brought together as the Blue Cross/Blue Shield of Michigan Cardiovascular Consortium (BCM2) Angioplasty Continuous Quality Improvement Project. Data points were defined, and a reporting mechanism was established. An active intervention was designed involving physician education, creation of provider working groups, and the use of specific bedside tools for patient management—similar to actions proposed in MSQC programs. Compared with baseline, the intervention group 4 years later had significantly higher use of preprocedural aspirin and glycoprotein IIb/IIIa blockers, lower use of postprocedural heparin, and a lower amount of contrast media administered per case. Outcomes improved dramatically as lower rates of transfusions, vascular complications, contrast nephropathy, stroke, and transient ischemic attacks were noted (P < 0.05).13-17 In another Michigan trial involving 108 intensive care units,
evidence based practice was used to reduce the incidence of blood stream infection. The intervention was highly successful; the mean rate of infection per 1000/catheter days decreased from 7.7 at baseline to 1.4 at 16 to 18 months of follow-up (P < 0.002). It seems reasonable to assume that such findings would be associated with lower hospital costs as well, which would also benefit the third party payer. It is important to note that the impressive results of the intervention were noted 3 months after the study began, and were sustained through the 15 subsequent months of the study.

Our calculations about the degree of improvement needed to offset the cost of ACS-NSQIP are hypothetical, but we believe they provide a framework for discussion as third party payers are offered the opportunity and encouraged to partner with providers. The combination of organized, regional quality interventions, guided by rigorous, comparative performance reporting, has great potential to improve quality and reduce costs in surgical care. The net result of such is that the provider-payer partnerships make good business sense. Although BCBSM/BCN has taken the lead so far, other large payers should be encouraged to establish and evaluate similar regional QI-focused strategic partnerships. Building on this experience, surgeons have an important opportunity to partner with regional and national payers in efforts to catalyze QI in surgery, with the most important results being better outcomes for a great many of our patients and decreased health care expenditures.

REFERENCES

The Quality of Trials in Operative Surgery

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Objective: This study aimed to assess the reported quality of trials in operative surgery.

Summary Background Data: Randomized controlled trials (RCTs) in operative surgery have previously been criticized for using weak methodology despite no evidence to suggest their quality is any different from nonsurgical trials.

Study Design: All surgical RCTs published in the British Medical Journal, the Journal of the American Medical Association, The Lancet, and the New England Journal of Medicine between 1998 and 2004 were identified. The adequacy of the reported methodology used to perform the randomization, power calculation, and recruitment was assessed for each trial using predefined criteria. The results from the surgical trials were compared with a randomly selected control group of nonsurgical RCTs, which were matched for journal and year of publication.

Results: Sixty-six surgical RCTs were identified. Adequate reporting of randomization sequence generation was seen in 42% (n = 28) of surgical trials and 30% (n = 20) of nonsurgical trials, and adequate allocation concealment was recorded in 46% (n = 30) and 47% (n = 31), respectively. When combining these 2 interrelated steps of randomization, only 26% (n = 17) of surgical trials and 23% (n = 15) of nonsurgical trials reported both adequately. Adequate recruitment was recorded in 52% (n = 33 of 63) surgical and 55% (n = 33 of 60) nonsurgical trials, with approximately a quarter (n = 17 and n = 16, respectively) of the trials in both the surgical and nonsurgical categories reporting an adequate power calculation.

Conclusions: There was no evidence that the reported quality of surgical trials was different to nonsurgical trials. However, approximately half or less of all the trials reviewed reported adequate methodology.

(Ann Surg 2007;246: 1104–1109)

Understanding and assessing the quality of research is an essential process in the appropriate application of evidence-based medicine. Randomized controlled trials (RCTs) are recognized as the gold standard for evaluating new clinical interventions. However, if the methodology employed in an RCT is suboptimal, the validity of the trial’s results may be lost, as is the suitability of the trial for entry into a systematic review or meta-analysis.

Surgical research has been criticized for using weak methodology because of the under-utilization of RCTs and the overuse of case series as a means of advancing surgical knowledge. Furthermore, the quality of surgical RCTs that have been undertaken has also been criticized. However, it is recognized that evaluating operative interventions presents a unique set of challenges to trial design. Issues that can impact on the quality of surgical RCTs include the learning curve associated with any new procedure, intersurgeon variation in operative technique, blinding, and lack of adequate funding. Yet there are some important methodological features in RCTs that are equally possible to implement and report in all trials regardless of their medical specialty. These include the process of randomization, use of appropriate power calculations, and attainment of adequate recruitment.

Randomization eliminates selection bias that can occur when patients are chosen to receive a specific treatment. The first step in maintaining the integrity of the randomization process is to ensure that the randomization sequence used is totally unpredictable, eg, using a computer-generated random numbers list. Often however, stratified randomization is used to ensure balance between the trial arms for important predictor variables. Minimization is one acceptable method of weighted randomization that can be used to balance known prognostic factors between trial arms. A second method is blocked randomization in which recurring blocks are used in patient allocation. However, use of blocks can introduce a predictable pattern of allocation into the randomization process. To prevent this, either randomly assorted blocks rather than systematically progressing lists can be used.

Once the randomization sequence has been generated, the allocation needs to be concealed from the recruiting clinician and the person ultimately responsible for administering the treatment (if different from the recruiting clinician) to avoid the conscious or subconscious introduction of bias. Commonly this is achieved by using an independent party to undertake the randomization process (eg, using telephone randomization).
Power (sample size) calculations should be carried out at the design stage of all trials. This vital step in trial planning guides recruitment to ensure that sufficient numbers are enrolled in the trial. Although under-recruiting reduces the power of a study, over-recruiting carries resource and ethical implications. The sample size (for any given significance level) is dependent on the effect size and the statistical power required. It is essential that the effect size used in the power calculation relates to a clinically relevant primary outcome of the study, and furthermore, the estimated expected effect size, or control-group event rate, is accurate to identify the minimal effect that is clinically relevant.

In this study we aimed to assess the reported quality of trials investigating operative surgery. We hypothesized that when comparing surgical and nonsurgical trials, there would be no difference in the reported quality of methods used to generate their randomization sequences, conceal allocation, calculate power, and meet recruitment targets.

**METHODS**

We identified all the RCTs found in 4 high-profile, peer-reviewed medical journals: *British Medical Journal, Journal of the American Medical Association, New England Journal of Medicine,* and *The Lancet,* published between 1998 and 2004 in the Cochrane Central Register of Controlled Trials (CENTRAL, www.cochrane.org). We deliberately used these journals, renowned for their high quality, for 2 main reasons: first our results represent a marker of “best” research and second surgical and nonsurgical trials from the same journal can be compared. The abstracts were screened to identify all the operative surgical trials by 2 independent reviewers who also undertook individual online hand searches of the journals for 2002, 2003, and 2004 to ensure no studies were missed through any gaps between their publication and the updating of the CENTRAL database.

An RCT was included in the “surgical trials” group if the “trial evaluated a procedure carried out by a surgeon in an operating theater where the intervention effects an alteration in the patient’s anatomy.” All other trials were taken to represent nonsurgical trials. From the 2289 trials in the “surgical trials” group, control RCTs matched by journal and year of publication were randomly selected by computer.

Exclusion criteria included trials with more than 2 arms, as some of these trials differed in the quality of methodology used between their different arms; cluster randomized trials methods for allocation concealment and power calculations can differ from standard trials and reports that did not represent the main analysis of the study.

The final recruitment levels and methodology used to produce the randomization and sample sizes, for each trial, were assessed for quality against predefined criteria (Table 1). Unlike some of the other areas of the trial methodology, such as blinding, these aspects of trial design were used, as they are equally achievable and reportable in all trials regardless of their medical specialty; furthermore, the standards of methodology used to employ them can be clearly defined and categorized. Hence, other areas of trial design, such as the appropriate use and application of intention-to-treat analysis, for example, was not examined in this study. Two independent assessors (C.W. and K.M.) performed all of the data collection separately and consistency between their results was assessed. Differences between the assessors were resolved by review and discussion.

The proportions of trials in each category were compared using a 2-sampled t test, which allows proportions to be compared while weighting by the number of articles and adjusting for clustering by journal. Analyses were carried out using Stata 8 (Stata Corp., College Station, TX).

**RESULTS**

The trials studied, grouped according to journal and article type, are shown in Table 2. The $\kappa$ scores of initial agreement between the 2 independent reviewers, before discussion and consensus was reached, were 1 for assessment of adequacy of sequence generation, power calculation, and recruitment and 0.82 for assessment of allocation concealment.

The number of surgical and nonsurgical trials reporting adequate sequence generation, allocation concealment, power calculations, and recruitment is shown in Table 3. No significant differences were found between the surgical and the nonsurgical trial groups in any of the categories assessed. However, over 50% of both the surgical and nonsurgical studies reviewed demonstrated either inappropriate or unclear reporting of sequence generation, allocation concealment, and power calculations. Trials that were classified as “unclear” did not contain adequate information within their report to classify them into adequate or inappropriate. Examples of unclear reporting for randomization sequence generation and allocation concealment are shown in Table 4. For the power calculation and recruitment data to be unclear, the criteria listed in Table 1 were incompletely reported such that an adequacy assessment could not be made.

**Sequence Generation**

Eleven (17%) surgical trials and 10 (15%) nonsurgical trials used random number lists to adequately generate their randomization sequences, and no trials reported randomizing using sequences derived from inappropriate methods such as alternation or based on patient’s date of birth. However, 18 (27%) surgical and 10 (15%) nonsurgical trials were unclear in their reporting of their sequence generation.

The remaining trials generated their sequences using techniques to constrain or stratify. Of these, 10 (15%) surgical and 4 (6%) nonsurgical trials used dynamic methods of randomization, and 27 (41%) and 42 (64%) trials, respectively, used blocked randomization. Within the blocked trials, 26% (7) of the surgical trials and 14% (6) of the nonsurgical trials reported an adequate use of blocks to prevent sequence prediction. Fifty-six percent (15 of 27) of surgical trials and 52% (22 of 42) of nonsurgical trials used techniques that we defined as inappropriate, and the remaining 19% (5 of 27) surgical and 33% (14 of 42) nonsurgical trials were unclear in the reporting of their application of blocked randomization.
Allocation Concealment

Of the 55% (36) of surgical trials whose allocation concealment did not meet adequacy, 20% (13) actually used inappropriate methodology and 35% (23) had unclear reports. Similarly, for the 53% (35) of nonsurgical trials, 12% (8) used inappropriate methods and 41% (27) were unclear.

Power Calculations

Fifty-four (82%) surgical trials and 46 (70%) nonsurgical trials provided enough data for the reader to reproduce the power calculation; however, in about half of all trials (56% (37) surgical and 47% (31) nonsurgical trials), it was not clear that the primary outcome was used within this...
TABLE 3. Surgical and Nonsurgical Articles Reporting Adequate Sequence Generation, Allocation Concealment, Power Calculations, and Recruitment

<table>
<thead>
<tr>
<th>Methodology Examined</th>
<th>Surgical RCTs (n = 66)</th>
<th>Nonsurgical RCTs (n = 66)</th>
<th>P (95% CI of Difference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate randomization sequence generation</td>
<td>28 (42%)</td>
<td>20 (30%)</td>
<td>0.40 (–20.4–44.6)</td>
</tr>
<tr>
<td>Adequate allocation concealment</td>
<td>30 (45%)</td>
<td>31 (47%)</td>
<td>0.89 (–29.8–26.6)</td>
</tr>
<tr>
<td>Adequate randomization sequence generation and allocation concealment together</td>
<td>17 (26%)</td>
<td>15 (23%)</td>
<td>0.81 (–26.8–32.9)</td>
</tr>
<tr>
<td>Adequate power calculation</td>
<td>17 (26%)</td>
<td>16 (24%)</td>
<td>0.80 (–12.7–15.8)</td>
</tr>
<tr>
<td>Adequate recruitment*</td>
<td>33 (52%)</td>
<td>33 (55%)</td>
<td>0.76 (–17.9–23.2)</td>
</tr>
</tbody>
</table>

*Interim analysis excluded; for surgical RCTs n = 63 and for nonsurgical RCTs n = 60.

CI indicates confidence interval.

TABLE 4. Examples of Reports Leading to an “Unclear” Categorization for Generation of Randomization Sequence and Allocation Concealment

<table>
<thead>
<tr>
<th>Area of Categorization</th>
<th>Examples of Text Leading to Unclear Categorization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomization sequence</td>
<td>“Patients were randomly assigned…”</td>
</tr>
<tr>
<td></td>
<td>“A randomization list with a block size of 4 was generated by the sponsor…”</td>
</tr>
<tr>
<td></td>
<td>“Patients who met the inclusion criteria were randomly assigned…”</td>
</tr>
<tr>
<td></td>
<td>“Patients were randomized…”</td>
</tr>
<tr>
<td></td>
<td>“Patients were randomized on arrival to theatre by selection of sealed envelopes…”</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>“Infants were randomly assigned…”</td>
</tr>
<tr>
<td></td>
<td>“Patients were randomized…”</td>
</tr>
<tr>
<td></td>
<td>“Patients were randomized on arrival to theatre by selection of sealed envelopes…”</td>
</tr>
</tbody>
</table>

calculation. This was because the trials failed to clearly define their primary outcome rather than trials using other outcomes to generate their power calculation.

Twenty-one (32%) surgical and 15 (23%) nonsurgical trials referenced a published source for the effect size used in their power calculations, with 4 (6%) and 7 (11%), respectively, referring to unpublished data. Thirty (45%) surgical and 36 (55%) nonsurgical trials used effect sizes that were not reported to be based on previous data.

Trial Recruitment

Adequate recruitment was recorded in just over half of all trials reviewed, of which only 10 (30%) surgical and 11 (33%) nonsurgical trials also had adequate power calculations (P = 0.79, 95% confidence interval of difference –30.4%–24.3% points). These figures were higher than the proportion of adequate power calculations seen among all the trials (adequately and inappropriately recruited), which was just 25%.

Two surgical trials that failed to meet adequate recruitment actually concluded that there was no significant difference between the control and intervention groups’ results for their sole primary outcome. Both of these studies did acknowledge this failure in their reports.

DISCUSSION

In this methodological review we found no statistically significant differences between the surgical and nonsurgical trials we compared from high-profile general medical journals. At the time of preparation of this work there were no previous studies comparing quality in surgical and nonsurgical trials and therefore we were unable to perform a prospective sample size calculation. Although this work offers important informative data addressing this issue, the reader should be aware that the small differences actually observed during the study is not adequately powered to confidently exclude a type 2 error. To increase the sample size to address lack of power gives the likely benefit of improved precision of the study (ie, smaller confidence intervals) but is unlikely to actually change the point estimates given, and in return, this additional precision would come at the cost of increased data contamination (through inclusion of reports from journals of poorer quality and increasing any temporal biases).

In over 50% of all trials examined during this study there were inadequacies with the quality of methodology and reporting used to generate and conceal the randomization sequence before allocation and generate their power calculations. Unfortunately we had insufficient numbers of trials in this study to investigate whether there was a temporal relationship with trial quality during the post-Consolidated Standards of Reporting Trials (CONSORT) period examined.

The CONSORT statement, developed in 1996 and revised in 2001, aims to address some of the problems associated with the quality of trial reporting. It clearly states that “methods used to generate the random allocation sequence, including any details of any restrictions,” “method used to implement the random allocation sequence,” and “how sample size was determined” should be stated.13
The tight word restrictions placed on authors by the journal editors may, in part, explain the “unclear” reporting of the trial methodology. Additionally, poor reporting may not mean that the quality of the study is also poor. However, for such fundamental methodological features of RCTs, clarity should be encouraged, especially given the use of RCTs in systematic reviews and meta-analysis in which quality assessment is vital.

A number of studies reviewed the use of “inappropriate” methods for allocation concealment. An association between such methodological deficiencies and trial results has been reported. For example, Schulz et al reported that of 250 RCTs, those with inadequate or unclear reporting of allocation concealment (allowing the potential for subversion) demonstrated an average treatment effect of 30% to 40% bigger than the adequately concealed trials.

There can be pressure on trialists to keep their sample sizes small, as this will have the advantage of reducing trial resources. One way of achieving smaller sample sizes is to look for a larger effect size. Interestingly 50% of the trials examined in this study failed to adequately justify the effect size used in their power calculations. However, when we examined those trials that adequately reached their recruitment targets, we found they tended to demonstrate a higher proportion of adequate power calculations than those trials that were under-recruited. These findings would not support the suggestion that the lack of clarity in power calculation and effect size reporting may be driven by a desire to demonstrate that adequate recruitment was reached.

Although this study examines the reported quality of randomization, power calculation, and recruitment, as these represent the methodological features and lend themselves to fair comparison between surgical and nonsurgical trials, being equally achievable in both, it leaves the assessment of quality of many of the other noncomparable areas of trial methodology untouched. These other methodological features, such as the learning curve associated with any new procedure, intersurgeon variation in operative technique, accommodating technical and operative advances that occur during the trials recruitment period, blinding, and patient preference, are harder to objectively assess, yet they may represent the real challenges that limit the quality of the surgical trial design. Although not examined in this study, adequate understanding and assessment of these wider methodological issues are needed to prevent misleading data arising from poor quality surgical trials being given inappropriate credibility.

This study used 4 high-quality medical journals to source the surgical and nonsurgical trial reports that it compared. The equivalence in quality of reporting our results demonstrated between these groups may reflect this, as only trials that met adequate standards to survive the rigorous review process these “elite” medical journals employ, were included. However, assuming that the standards of trial review are constant for any particular general medical journal, regardless of the trials subject matter, this methodological bias will always occur when reviewing work in peer-reviewed journals. It is possible that the quality of both surgical and nonsurgical trials reported in these general medical journals may not represent the quality seen in specialty-specific journals. A similar study has shown that surgical trials in leading general health-care journals are better in quality than that in the leading surgery-specific journals; however, whether the same is true for nonsurgical trials is unclear. It would be interesting to compare the data of these studies for surgical trials with a matched group of “nonsurgical trials”; however, the inevitable difficulties, and potential for bias, associated with identifying appropriately matched trials from subject-specific journals would occur. Perhaps a study comparing a series of surgical and nonsurgical trials at completion, but before their submission to a medical journal, would give a truer reflection of differences in the actual quality of trial methodology currently being employed. Nonetheless in both the surgical and nonsurgical trial groups we studied there were substantial proportions not reporting adequate allocation concealment, sequence generation, power calculations, or recruitment. To ensure the use of solid evidence to inform both surgical and medical practice, it is important that all trials use and report rigorous methods.

REFERENCES


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Little Science, Big Science
Strategies for Research Portfolio Selection in Academic Surgery Departments

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Objective: To evaluate National Institutes of Health (NIH) funding for academic surgery departments and to determine whether optimal portfolio strategies exist to maximize this funding.

Summary Background Data: The NIH budget is expected to be relatively stable in the foreseeable future, with a modest 0.7% increase from 2005 to 2006. Funding for basic and clinical science research in surgery is also not expected to increase.

Methods: NIH funding award data for US surgery departments from 2002 to 2004 was collected using publicly available data abstracted from the NIH Information for Management, Planning, Analysis, and Coordination (IM PAC) II database. Additional information was collected from the Computer Retrieval of Information on Scientific Projects (CRISP) database regarding research area (basic vs. clinical, animal vs. human, classification of clinical and basic sciences). The primary outcome measures were total NIH award amount, number of awards, and type of grant. Statistical analysis was based on binomial proportional tests and multiple linear regression models.

Results: The smallest total NIH funding award in 2004 to an individual surgery department was a single $26,970 grant, whereas the largest was more than $35 million comprising 68 grants. From 2002 to 2004, one department experienced a 336% increase (greatest increase) in funding, whereas another experienced a 73% decrease (greatest decrease). No statistically significant differences were found between departments with decreasing or increasing funding (greatest decrease). No statistically significant differences were found between departments with decreasing or increasing funding, whereas another experienced a 73% decrease (greatest decrease).

Conclusions: Although incentives to junior investigators and clinicians with secondary participation in research are important, our findings suggest that the best strategy for increasing NIH funding for surgery departments is to invest in individuals with focused research commitments and established track records of garnering large and multiple research grants.


The fiscal year 2006 National Institutes of Health (NIH) budget was $28.845 billion, an increase of only 0.7% compared to the previous year; this was the least in nearly 4 decades. A similar 0.8% increase is estimated for 2007. This is particularly alarming given that NIH applications for research project grants (RPGs) have increased 2-fold over the last 9 years, with the average size of each RPG increasing nearly 40%. As the NIH budget seems to be growing at a rate disproportionately lower than the number of RPG applications, it is imperative that research institutions evaluate their strategies for optimizing research funding for their respective departments.

From 1995 to 2001, the 5 clinical departments at US medical schools with the highest number of NIH grant submissions were in order, medicine, psychiatry, pediatrics, surgery, and neurology. However, surgical grant proposals were significantly less often funded when compared with nonsurgical submissions, and when successful, were associated with smaller award sizes. Although there is an abundance of evidence suggesting that research activity among clinician-scientist surgeons is decreasing, it remains unclear why certain surgery departments receive significantly
fewer awards and lesser total funding than others. It is possible that larger, more funded departments differ in the types of grants awarded or in the balance of funding for basic science versus clinical research.

In this study, we tested the hypothesis that departments with a greater proportion of R- and K-type grants, and hence large research projects and young investigator support, experienced a more significant increase in funding from 2002 to 2004. In doing so, we examined NIH funding of academic surgery departments during this period. Specifically, we compared portfolio strategies regarding distribution of research effort across scientific fields (basic and clinical), grant type, as well as the concentration of awards with large dollar amounts (Big Science) versus a large number of smaller awards (Little Science).8

METHODS

Data regarding NIH funding awards to US surgery departments during 2002 to 2004 were collected using publicly available information from the NIH Office of Extramural Research website,9 which contains selected grant data abstracted from the Information for Management, Planning, Analysis, and Coordination (IMPAC) II database.10 On its website, the Office of Extramural Research provides detailed information regarding specific funding mechanisms awarded to surgery departments.11,12 Data from 2005 and onwards is currently unavailable. A total of 88 institutions that received NIH funding in 2002 for surgery were analyzed in all 3 years; no institutions were excluded. From this data, we established a list of institutions according to the following categories: 5 programs with the greatest NIH funding (absolute dollars), 5 programs with the least funding, 5 programs with the largest increase (absolute dollars) in total awards, and, finally, 5 programs with greatest decrease in total awards. This list was formulated by sorting and evaluating the data based on award size, and by calculating the change in total funding awarded to surgical departments in 2002 compared with 2004 for each institution.

We subsequently used the online Computer Retrieval of Information on Scientific Projects (CRISP) database13 to create a spreadsheet listing all grants awarded to surgical departments for each of the 20 institutions identified above, encompassing the years 2002 to 2004. Briefly, CRISP contains information regarding all research projects and programs supported by the US Department of Health and Human Services, including the NIH, Food and Drug Administration, Centers for Disease Control, and other government agencies. Only NIH data from the CRISP database was used in this study. In searching the database, search terms such as urology, otorhinolaryngology, neurology (and other surgical subspecialties) did not yield results that did not use the term “surgery.” However, our CRISP database query for “orthopedic” frequently yielded funding results that did not contain the term “surgery,” but were clearly surgical grants. Thus, the final search query consisted of the terms “surgery,” “surgical,” or “orthopedic” together with the years of interest. All search results were reviewed individually: only grants with the word “Surgery” listed for “Department” were recorded. However, to capture grant awards that did not contain the terms “surgery,” “surgical,” and/or “orthopedic” in their abstract description, and thus would not be included in the initial search results, a second query was done using the CRISP “Institutes and Centers” search criteria function.13 The following NIH entities were simultaneously selected for this query: Allergy & Infectious Diseases; Arthritis & Musculoskeletal & Skin Diseases; Cancer; Center for Disease Control & Prevention; Child Health & Human Development; Dental & Craniofacial Research; Diabetes & Digestive & Kidney Diseases; General Medical Sciences; Health Resources and Services; Heart, Lung & Blood; Library of Medicine; Neurologic Disorders & Stroke; Nursing Research; National Center for Complimentary and Alternative Medicine; and Research Resources. We repeated the above CRISP search procedures for all 15 institutes for the years 2002 to 2004.

For all surgical grants yielded by our CRISP queries, we recorded the grant number, first and last name of principal investigator, e-mail address of principal investigator, project title, abstract description, institution receiving award, fiscal year, and thesaurus terms. For the purposes of statistical analysis, each grant was classified into subcategories (basic versus clinical/translational; clinical research subcategory; grant type) based on its thesaurus terms. Only those grants with the thesaurus terms “human,” “clinical,” or “patient” were initially classified as clinical/translational research by the investigators. Each grant was then inspected individually by 2 of the investigators to verify whether in fact the grant was best classified as “clinical/translational” or “basic” science. Both basic and clinical/translational research was further categorized according to specialty of research (Table 1). In addition, the funding mechanism (Table 2) was identified.

TABLE 1. Clinical and Basic Science Subspecialty Research Categories

<table>
<thead>
<tr>
<th>Categories</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer/neoplasm/metastasis</td>
</tr>
<tr>
<td>Hepatitis/intestine/liver/stomach/esophagus/pancreas</td>
</tr>
<tr>
<td>Transplant/organ failure/end-stage</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Heart/cardiac/vascular/atherosclerosis/stroke/myocardial infarction</td>
</tr>
<tr>
<td>Cardiovascular</td>
</tr>
<tr>
<td>Musculoskeletal/arthritis/skin/bone/cartilage/ligament</td>
</tr>
<tr>
<td>Trauma/sepsis/critical care/SIRS/hemorrhage/shock</td>
</tr>
<tr>
<td>Alternative medicine/complementary medicine/traditional medicine/herbal</td>
</tr>
</tbody>
</table>

TABLE 2. Operational Definitions of NIH Funding Awards14

<table>
<thead>
<tr>
<th>Funding Mechanism</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>Research projects</td>
</tr>
<tr>
<td>K</td>
<td>Research career programs</td>
</tr>
<tr>
<td>F</td>
<td>Fellowship programs</td>
</tr>
<tr>
<td>T</td>
<td>Training programs</td>
</tr>
<tr>
<td>P</td>
<td>Research program projects and centers</td>
</tr>
<tr>
<td>U</td>
<td>Cooperative agreements</td>
</tr>
</tbody>
</table>
for all basic and clinical awards based on the unique grant number for each award.14

Statistical Analysis

Data were tabulated in a Microsoft Excel (Microsoft Corporation, Redmond, WA) spreadsheet and analyzed using GNU-R and Intercooled Stata 10 (Stata Corporation, College Station, TX). Statistical analysis was based on binomial proportional tests and multiple linear regression models, all calculated with 95% confidence intervals.

Dependent variables included the distribution of research fields, total dollars per investigator, total dollars per grant, and the number of T-, P-, U-, F-, R-, and K-type grants across institutions. Binomial proportion tests were used to compare departments according to the magnitude of decrease or increase in research funding from 2002 to 2004 (5 departments with the most significant decrease in funding vs. those 5 with the most significant increase). Outcomes in regression modeling included total dollars per department, total number of grants, change in dollars from 2002 to 2004, and the proportion of funding from different grant type. Multiple linear regression models with splines with and without polynomials were used to model the relationship between change in dollars between 2002 and 2004 and both total dollar amount per grant and total dollar amount per investigator. \( \chi^2 \) tests were used to test the association between proportion in grant type between top increasing and bottom decreasing departments.

RESULTS

Study Sample

Our study included an analysis of 87 academic US surgery departments that received NIH funding from 2002 to 2004. The smallest total NIH funding award in 2002 to an individual surgery department was a single $72,250 grant, whereas the largest was more than $35 million comprising 56 grants. The smallest total NIH funding award in 2004 to an individual surgery department was a single $26,970 grant, whereas the largest was more than $35 million comprising 68 grants. During this interval, one department experienced a 336% increase (greatest increase) in funding, whereas another experienced a 73% decrease (greatest decrease). The absolute decreases/increases in funding are depicted in Table 3.

Scientific Fields

Comparing departments according to the magnitude of decrease or increase in research funding from 2002 to 2004 (5 departments with the most significant decrease in funding vs. those 5 with the most significant increase), there were a total of 193 and 443 awards in 2002 to 2004 in each group, respectively. Both groups had similar proportions of funding awarded for basic science and clinical/translational science (Fig. 1). Similarily, there were no differences between these 2 sets of departments in funding awarded toward different basic or clinical subspecialties. Of the 636 awards in both groups, 73 (11.5%) could not be categorized as either purely basic or clinical/translational science by 2 of the investigators.

Little Science, Big Science

Compared with departments who experienced a decrease in funding, those experiencing the most drastic increase (total dollars) in funding had a greater proportion of type U (\( P = 0.01 \)) and type F grants (\( P < 0.01 \)), smaller proportion of K grants (\( P = 0.03 \)), and greater absolute

<table>
<thead>
<tr>
<th>Surgery departments with the greatest decrease in funding*</th>
<th>Change in Total Award Size</th>
<th>Change in Number of Grants</th>
<th>Percentage Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>$4,573,481</td>
<td>-14</td>
<td>-31.24</td>
<td></td>
</tr>
<tr>
<td>$2,147,657</td>
<td>-3</td>
<td>-54.71</td>
<td></td>
</tr>
<tr>
<td>$1,907,495</td>
<td>0</td>
<td>-52.65</td>
<td></td>
</tr>
<tr>
<td>$1,867,814</td>
<td>2</td>
<td>-39.51</td>
<td></td>
</tr>
<tr>
<td>$1,693,969</td>
<td>-7</td>
<td>-73.29</td>
<td></td>
</tr>
</tbody>
</table>

Surgery departments with the greatest increase in funding:

<table>
<thead>
<tr>
<th>Surgery departments with the greatest increase in funding*</th>
<th>Change in Total Award Size</th>
<th>Change in Number of Grants</th>
<th>Percentage Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>$5,952,669</td>
<td>0</td>
<td>142.55</td>
<td></td>
</tr>
<tr>
<td>$5,919,095</td>
<td>6</td>
<td>192.66</td>
<td></td>
</tr>
<tr>
<td>$5,714,045</td>
<td>6</td>
<td>149.24</td>
<td></td>
</tr>
<tr>
<td>$5,043,941</td>
<td>12</td>
<td>336.89</td>
<td></td>
</tr>
<tr>
<td>$4,705,997</td>
<td>6</td>
<td>148.24</td>
<td></td>
</tr>
</tbody>
</table>

*Sorted by change in award size.

FIGURE 1. Proportion of NIH-funded research portfolio according to basic and clinical/translational science categories. The 5 programs that experienced the greatest increase in funding had a total of 443 awards from 2002 to 2004: 299 basic science, 93 clinical/translational science, and 51 others. The 5 programs that experienced the greatest decrease in funding had a total of 193 awards: 133 basic science, 38 clinical/translational science, and 22 others. \( P \) values represent comparison among the 5 programs that experienced the greatest increase versus those 5 that experienced the greatest decrease in NIH funding.
number of R grants (292 vs. 120). There was no difference in the proportion of R, T, or P type grants between these 2 groups of institutions (Fig. 2). Ten (1.6%) of the combined 636 awards in both groups were not classified according to standard NIH award categories. From 2002 to 2004, a linear association between amount of decrease/increase in total department funding was found with both the average amount of funding per grant and funding per investigator \((P < 0.01)\), suggesting that departments that increased their total funding relied on investigators with large amounts of funding per grant (Fig. 3).

**DISCUSSION**

We found no difference in the proportion of research funding devoted to basic and clinical disciplines in surgery departments with the greatest increase in total NIH funding (total dollars) compared with those with the most substantial decrease. Programs with the most remarkable increase in funding had a larger percentage of their portfolio derived from U and F grants. Interestingly, there was no difference in the proportion of funding derived from R grants between these programs. However, our results suggest that the total number of R grants correlates with total surgery department funding: Big Science strategies (a focus on larger R awards typically pursued by faculty members dedicating most of their time to research activities as opposed to clinical practice) are associated with a higher likelihood of positive changes in total dollar amount in federal funding.

There is an increasing need for surgery departments to evaluate their strategies for optimizing research funding, especially with recent NIH budget cuts: surgery departments seem to be less successful in securing funding compared with other medical specialties.5,15,16 There are several plausible explanations for why NIH funding for surgery-related research has lagged behind other medical fields. It has been demonstrated that surgeons are less active in the peer-review process compared with other physicians.5,17 Therefore, it is not surprising that over 50% of surgery-related NIH grants are reviewed by “nonsurgical study sections”.17 It has been suggested that this phenomena among surgeons can be ascribed, in part, to a greater proportion of time devoted to clinical responsibilities over research compared to nonsurgeons.5 This balance for surgeons between research and clinical time appears to be increasingly tilted towards the latter.6,7

Across all medical disciplines, funding for clinical research has lagged behind awards for bench research.18 This is likely a function of the demographic of researchers who have been successful in securing funding: the number of first time grant applications to the NIH by “MD-only” scientists, though increasing, is far less than all PhD researchers combined (PhD only and MD-PhD applicants).17,18 Compared to these 2 groups, MDs have competed less successfully for funding over the past 30 years.19 This lag in clinical research funding has been particularly alarming in surgery. Notably, the composition of NIH study sections for clinical research in surgery may contribute to the success of submitted grant applications. It has been suggested that these sections are

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**FIGURE 2.** Proportion of NIH-funded research portfolio according to funding mechanism (ie, grant type). The 5 programs that experienced the greatest increase in funding had a total of 443 awards from 2002 to 2004: U grants comprised 28 awards, T = 24 awards, R = 292 awards, K = 47 awards, F = 16 awards, P = 31 awards, other = 5 awards. The 5 programs that experienced the greatest decrease in funding had a total of 193 awards: U grants comprised 3 awards, T = 14 awards, R = 120 awards, K = 45 awards, no F awards, P = 6 awards, other = 5 awards. \(P\) value represents comparison among the 5 programs that experienced the greatest increase versus those 5 that experienced the greatest decrease in NIH funding.

**FIGURE 3.** Change in NIH funding from 2002 to 2004 versus total dollars/grant depicted using spline analysis. Data from all grant types are included. After performing regression diagnostics, the linear regression model presented the best fit compared with log-transformed distributions. The \(P\) value for the trend is <0.01.
commonly composed of comparatively inexperienced reviewers, often younger surgeons who tend to be overly “critical” in the peer-review process. These sections also do not reflect the spectrum of surgical subspecialties; instead they are heavily represented by transplant and cardiothoracic surgeons. Although surgery funding has decreased, productivity in the basic sciences remains relatively promising. Nonetheless, despite a mean annual increase of 9.5% in the number of basic science articles from Departments of Surgery compared with 1.5% from Departments of Medicine from 1992 to 1999, funding for surgery research increased only 3.1% compared with 21.1% for medicine.

We found no difference in the proportion of either clinical ($P = 0.40$) or basic ($P = 0.93$) research funding among programs with the most significant gains (in dollars) compared with those that most substantially lost funding. Nonetheless, as both clinical and basic awards for surgery lag behind other specialties, it is imperative that departments develop strategies to maximize their research funding. In 2003, 56% of NIH funding (which comprised 44% of grants) to family medicine departments was awarded to only 7 institutions. R-type grants represented 72% of all awards (RO1 grants were 44% of all grants), with K- and U-type grants comprising 15% and 3% of all awards, respectively. Interestingly, most family medicine departments with more than 1 K award also had an RO1 award (4 of 5 departments). These findings suggest that a select few family medicine departments have been relatively more successful in securing funding from the NIH compared with most others, with multiple K awards likely to be granted to departments with an R award. However, we found no such association in our analysis of surgery departments.

Our results demonstrate that, to increase funding from the NIH, surgery departments must actively pursue researchers who can successfully compete for larger grants. This is especially true given that funding for NIH investigator-initiated grants (RO1), particularly for MD and MD/PhD applicants, has declined. Our findings suggest that surgery departments with greater funding per grant and funding per investigator have greater total departmental NIH funding. Although our results suggest that surgery departments who increased their total NIH funding from 2002 to 2004 had researchers who produced a high ratio of dollars/grant, it is impossible to conclude where these researchers lie on the spectrum of clinical-only versus research-only activity. In other words, there is, in fact, a wide spectrum of individuals between “pure” clinician surgeons and “pure” nonclinical investigators. In addition, surgery departments with the greatest gains in research funding had a greater absolute number of R grants in their research portfolios. These grants are usually awarded to the career researcher who has devoted much of his/her time to scholarly pursuit, often at the expense of clinical activity. Are the days of the triple threat—clinician, researcher, and educator—necessarily over? To develop a successfully funded academic surgery department, we believe that surgery departments should focus their efforts on recruiting a greater proportion of physician-scientists to increase their departmental research funding. Nevertheless, many obstacles exist for early career surgeon-researchers: despite a remarkable increase in the number of new investigators applying for grants, surgeons are significantly less successful in securing funding (K08, K23, and K24 grants) than non-surgeons.

One of the primary limitations of this study was the lack of detailed funding data available by investigator. Such data would better demonstrate a detailed portfolio profile for each department. In addition, although 2 investigators examined each grant closely to categorize it as a “clinical/translational” or “basic” award, there is much room for interpretation as some grants clearly have components of both types. It is important to note that the total size of NIH awards to an institution not only depends on the number and size of individual grants, but also the success of individual investigators in submitting proposals that are funded. Unfortunately, we do not have data regarding the “success rate” of individual institutions in being awarded NIH funding (eg, total number of grants awarded/submitted). Our conclusions are limited to the 3-year interval studied; we evaluated trends in funding over this limited interval, as older data were not available. As NIH funding for surgery likely correlates with total institutional awards, strategies for increasing departmental funding must be evaluated with decisions to increase funding for the institution.

Clinical and research endeavors are not mutually exclusive; they are 2 complementary surgical pursuits that enhance patient care. NIH-funded research not only benefits institutional research activity, but also clinical surgery and education as well. Clinician-scientists in surgery certainly can compete successfully for research funding; our results suggest that departments with the most substantial increase in funding had a greater number of large grants. In the current funding environment and rapid evolution of scientific knowledge and techniques, clinician-scientists will need to devote more time to research or collaborate as part of a larger research group to be competitive with and relevant to the larger research community. Although incentives to junior investigators and clinicians with secondary participation in clinical research are important, our findings suggest that the best strategy for increasing surgery department research funding is to invest in individuals with focused research commitments and established track records of garnering large and multiple research grants. The era of the small surgical laboratory is over.

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Does a Biologic Prosthesis Really Reduce Recurrence After Laparoscopic Paraesophageal Hernia Repair?

The recent article of Oelschlager and colleagues outlines the important problem of recurrent hernia following laparoscopic paraesophageal hiatal hernia repair.1 They are to be commended for performing a randomized trial comparing a biologic prosthetic reinforced repair using small intestinal submucosa (SIS) to a “primary repair” (1°). We have the following comments and questions:

Patients

We could not ascertain from the paper the number of patients screened, number eligible for the study, or number consenting. Full disclosure of these details, which can reveal possible biases of ascertainment, is increasingly becoming a criterion of a high-quality randomized trial. We would be interested in a full CONSORT diagram of the study, if for no other purpose than to permit its future inclusion in metaanalyses of this important subject.2

Analysis

The primary endpoint (hernia recurrence) was analyzed at 6-month intervals an unstated number of times, and no indication is given that these multiple interim analyses were accounted for in either initial sample size determination or interim stopping rules.3,4 What we do know is that the study was stopped before the predetermined goal of 71 patients per arm was reached, presumably because a statistically significant difference between the groups was found at interim analysis. At least 2, and possibly 8, interim analyses could have been performed before the final statistical testing was done that resulted in P = 0.04. To illustrate the problem of multiple interim analyses, suppose the probability of a true negative result (no statistically significant difference) is 0.95 for a single test. If 2 interim analyses are performed, this probability is 0.95 × 0.95 = 0.90, and the chance of false positive results rises from 5% to 10%; 4 interim analyses lower the chance of detecting a true negative result to 0.81 and of detecting a false positive to 19%. Therefore, we suspect that in this report, the finding of a difference between the study groups at P = 0.04 is actually not statistically significant. We therefore ask the authors what their stopping rule was, how this was reflected in the sample size calculations, and whether they adjusted their P values for these interim analyses. We understand that stopping rules can be complex in clinical trials, but in one way or another, one has to “pay” for them.

Follow-up

The reported prevalence of recurrent hiatal hernia at 6 months postoperatively as detected by barium swallow was 4 (9%) for SIS and 12 (24%) for 1°. However, barium swallow was not performed in 13 patients, 2 of whom died in the early postoperative course. Although not stated, it can be roughly calculated that 6 or 7 of 51 (12% or 14%) SIS patients and 4 or 5 of 55 (7% or 9%) living 1° patients did not have testing. Therefore, the range of recurrence is 8% (4 of 51) to 22% (11 of 51) for SIS and 21% (12 of 57) to 33% (19 of 57) for 1°.

Did the study design anticipate the possibility of death and noncompliance with follow-up?

Significance of 6-Month Follow-up

Recurrent hiatal hernia after laparoscopic repair of paraesophageal hernia is reported to increase with time.5 Is 6-month follow-up clinically sufficient? Are there plans for further follow-up and analysis by time-related methods?

Complications and Deaths

The authors state in the introduction that “Traditionally, paraesophageal hernias were repaired by thoracotomy or laparotomy with morbidity around 20% and mortality of 2%.” The reported morbidity for SIS in this randomized study was 24% and mortality was 0%, with an upper 95% confidence interval of 1.7%.

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To the Editor:

In the article “Prophylactic ilioinguinal neurectomy in open inguinal hernia repair: a double-blind randomized controlled trial” (Ann Surg. 2006;244:27–33), the anatomy of the ilioinguinal nerve (in the Materials and Methods section) has not been described correctly. This is a crucial point because the authors propose to transect this nerve to reduce chronic postoperative inguinal pain. This incorrect description interferes with interpretation of the results, and probably is the reason for the authors’ unusual high rate of pain. As far as we know none of the peringuinal nerves (iliohypogastric and ilioinguinal nerves, genital branch of genitofemoral nerve) enter the rectus muscle at any level. In this respect, the authors also mention “medially” (“. . . and medially to where it entered the rectus muscles”). This might imply that the authors are referring to the iliohypogastric nerve instead of the ilioinguinal nerve, as the former runs medially, whereas the latter runs along the spermatic cord, leaving the inguinal canal through the outer inguinal ring in a more lateral direction.

We consider it crucial to use correct descriptions of nerves for correct interpretation of this trial.

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Prophylactic Ilioinguinal Neurectomy in Open Inguinal Hernia Repair

A Double-blind Randomized Controlled Trial
We appreciate the interest of Drs. Rice and Blackstone in our recently reported study on the use of a biologic prosthesis in the laparoscopic repair of paraesophageal hernias (PEH). Their questions allow us to expand on several important areas regarding the design, conduct, and interpretation of our study.

In this multicenter trial, each investigating site approached all patients who met inclusion criteria for the study. Although the majority of patients invited agreed to participate, some, for a variety of reasons, chose not to. We did not specifically track these patients or their outcomes because the treatment provided was the standard for each center (the use and type of mesh was dictated by the surgeon's practice) and upper gastrointestinal series were not necessarily performed 6 months after the procedure as mandated by our trial. We have no reason to believe that these patients had any special reason why their potential inclusion in the study would have varied the outcome.

The next issue raised was the rationale for the use of interim analysis, the timing of such analysis, the potential bias introduced by such analysis and our rationale for ending the study at the time we did. During the planning phase of our trial, the investigators agreed that the outcomes would be reviewed every 6 months. The 2 drivers that led us to this decision were patient safety (the potential for unforeseen complications with the use of the biologic prosthesis) and the concern for potentially withholding the best treatment from a patient if a clear benefit was detected at an earlier time. The decision to conduct analysis at 6 months was based on several reasons. First, other studies have shown that most recurrences after paraesophageal hernia repair occur early. Second, since SIS is rapidly remodeled so that the strength of the native mesh deteriorates within the first week, we expected to see the effects of this on recurrence rates within the first 6 months of repair. Third, a study of a relatively uncommon condition, like PEH, takes substantial time to accrue patients (in our case 3 years); thus, a longer follow-up for the primary outcome variable would substantially extend the cost of the study, rendering it impractical and perhaps impossible to do.

The first two 6-month analyses were limited to complication rate (interventions, infection, dysphagia rates, and perforations). This was important to enhance safety for our patients, since little formal anatomic follow-up data existed. Thereafter, recurrence rates and complication rates were analyzed, with a plan to stop the trial if either were significantly higher. In doing so, 5 interim analysis of recurrence rates were performed, each with the same trend in recurrence rates as the final analysis reaching our agreed upon statistical significance (considered as a single analysis and not adjusted). Moreover, the noncompliance of 13 patients (who did not undergo the planned UGI at 6 months) and the 2 patients who died were definitely taken into account when our biostatistician (NP) was calculating the P values. We agree with Drs. Rice and Blackstone that interim analysis can increase the likelihood of a false positive finding. On the other hand, patient safety, the potential withholding of a better treatment, and the moral, ethical, and professional implications associated with not doing it led us to design the trial in the fashion it was.

The decision to stop the trial when we did was based on the combination of a significant benefit by the application of the biologic prosthesis and the lack of any side effects or complications attributable to it.

We agree with Dr. Rice, and in fact emphasized in the manuscript, that we do not know whether the short-term benefits in recurrence rates confer long-term protection of recurrence. Because we are extremely interested in knowing the long-term results, we are currently planning a follow-up study of these patients.

On the other hand, we disagree with Dr. Rice’s comments regarding the use of laparoscopy as the preferred approach in these patients. This study was not designed or meant to compare the laparoscopic to an open approach in the repair of paraesophageal hernias. Whereas this topic of “open versus laparoscopic” continues to be occasionally debated, the majority of surgeons treating this disease converted to a laparoscopic approach because of the recognized reduction in patient morbidity and the faster recovery when compared with laparotomy or thoracotomy. As for the incidence of complications reported in our study we should make clear that we counted as such any perioperative event that deviated from the normal. As a consequence, pneumothorax accounted for 82% of our complications. Pneumothorax resulted in all patients from breaches of the parietal pleura during the dissection of the large paraesophageal hernia sac, which are far easier to identify (and perhaps occur with higher frequency) when using laparoscopic techniques to repair this type of hernia. On the other hand, pneumothorax required no treatment (other than temporary reduction of intra-abdominal pressure intraoperatively), and disappeared rapidly after the operation. By contrast, a breach of the pleura occurs in 100% of patients treated by thoracotomy and requires a chest tube in all. So, although we did not intend this study to compare approaches, its results, particularly the in-
Mental Training in Surgical Education

To the Editor:

I enjoyed reading the recent article by Immenroth et al1 in the March issue of Annals of Surgery. As an up-and-coming general surgery intern, I am eager to learn about the various ways junior surgeons are being trained to become proficient in minimally invasive surgical procedures.

It would be quite interesting to see this mental training study applied to a younger, more novice group of surgeons. Current participants were an average age of 32 and had performed on average 10 to 12 laparoscopic procedures before this study. Also, these surgeons had graduated around 3 years before this additional training. Although these participants were undergoing a basic laparoscopic training course, I believe the group receiving mental training would be more apt to fully use this additional assistance merely due to the fact that they had more clinical and operative experience than a truly junior surgeon. Perhaps, the total number of operations performed, whether laparoscopic or not, should also have been provided in the study. It is possible that surgeons who have performed a greater number of operations of any type are more used to mentally walking through defined aspects of the procedure merely due to repetition and experience, and therefore, have a greater ability to extract and process the mental training exercise.

Another study by Andreatta et al attempting to improve the laparoscopic skills of 10 surgical interns (Lap Mentor Training, LMT, n = 10; CTL, n = 9) used the Lap Mentor high-fidelity, computer-aided simulations. The LMT took place within the first 2 months of internship while each subject denied prior use of simulation and reported 0 to 5 hours per week video game play currently as well as during childhood. The results showed that the LMT outperformed the control group in a subsequent animal-model operating room assessment (20 kg anesthetized male pigs). LMT completed both 30° camera navigation and eye-hand coordination exercises with greater accuracy and in significantly less time. In addition to the operating tasks, LMT outperformed the control group, who received no additional training, on a global rating scale (GRS) assessing camera navigation skills, efficiency of motion, instrument handling, perceptual ability, and safe electrocautery (mental training showed no additional benefit in the GRS when compared with the practical training group). The small sample size and the lack of assessment of a complete surgical procedure (laparoscopic cholecystectomy) do indeed take away from this study, but I believe it supports the role of virtual reality simulation in surgical education, especially for junior level surgeons. These interns were able to visualize and execute various tasks on the Lap Mentor (perhaps mimicking the internal obsessive and ideometric mental training phases) and subsequently outperformed the CTL group on the majority of the GRS.

Clearly, these new simulation techniques are becoming an increasingly important part of surgical training, whether for practicing surgeons or for new surgeons-in-training. Further research is needed to determine the optimal dose and timing of these educational interventions.

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mental processes and operations (eg, labyrinth task) and a motor task demands in particular coordination, stamina, power or strength (eg, balancing act, marathon, or weight lifting). Taking this into consideration, it could be hypothesized that the more a task demands cognitive skills, the successful application of mental training by a novice is more likely. Vice versa, the more a task requires motor skills the higher the level of experience should be to make an improvement probable (already showed in the metaanalysis by Driskell et al²).

Since a surgical procedure can be seen as an archetypal example of a task with high cognitive and motor components, mental training in surgery should be useful for novices and intermediate learners as well as for advanced surgeons. Therefore, we totally agree with Dr. Mukherjee in the conclusion that surgeons who have performed a greater number of operations are more used to “mentally walking through defined aspects of a procedure” (many thanks for this wonderful expression!) and have a greater ability to extract and process the mental training exercise. Yet, we also think that even surgical beginners could benefit from mental training because this kind of psychologic rehearsal leads especially to an improvement in cognitive tasks as, for example, our randomized controlled trial and the metaanalysis of Driskell et al² and Feltz and Landers³ showed. As Dr. Mukherjee mentioned, further research is needed to determine the optimal timing of these educational interventions.

We also totally agree with the idea of an affinity between mental and virtual reality training because both kinds of training methods are a form of predominately cognitive simulation, one driven by the person himself based on an operation primer (ie, mental training) and other driven by a special software program (ie, virtual reality training). Therefore, we’ve run a randomized controlled trial with pre–post–design about the effects of the Lap Mentor training (LMT) with 81 surgical residents since last year comparing LMT with training at the Box-Trainer (BT) containing a porcine organ model and with no training (NT) (Immenroth et al, in preparation). As in our study about mental training, we have used the same modified version of OSATS (Objective Structured Assessment of Technical Skills) as well as the Lap Mentor software directly (criteria: time, movements of left hand, movements of right hand, perforations, safe clipping, safe cutting, and safe cautery) to assess pre- and post-test performance of all 3 groups on the Lap Mentor and the Box-Trainer. As hypothesized, results yielded differences in improvement between pre- and post-tests in favor of LMT (even in the BT tests). But we are not able to explain to what extent the surgeons who were educated with LMT really mimicked the internal observative and ideomotoric mental training phases as Dr. Mukherjee wrote. Although it is quite reasonable to reason like this, the question about a possible affinity between mental and virtual reality training is still open and could only be answered in our opinion with a study that includes mental and virtual reality training.

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