Editor's comment
Online publication date: 24-Mar-2005

Comments

723 Robotic urology in the UK: establishing a programme and emerg

Prokar Dasgupta, Ashok Hemal, Kirsten Rose, the Guy's and St.

Online publication date: 24-Mar-2005

724 Laparoscopic reconstructive urology

Sravanti P. Tegavarupu, Prokar Dasgupta

Online publication date: 24-Mar-2005

726 Drug-eluting biomaterials in urology: the time is ripe

Bodo E. Knudsen, Ben H. Chew, John D. Denstedt

Online publication date: 24-Mar-2005

727 The European working-time directive: one step forward, two st

Majid Shabbir, Peter Amoroso, Roger S. Kirby

Online publication date: 24-Mar-2005

Mini-reviews

729 Peyronie's disease: the epidemiology, aetiology and clinical eval

Christopher J. Smith, Chelsea McMahon, Ridwan Shabsigh

Online publication date: 24-Mar-2005

733 Recent advances in understanding the biology of diabetes-associ and novel therapy

Naoki Yoshimura, Michael B. Chancellor, Karl-Erik Andersson

Online publication date: 24-Mar-2005
Molecular prognostic factors in bladder cancer
Maurizio Buscarini, Marcus L. Quek, Parkash Gill, Guangbin Xia, David I. Quinn, John P. Stein
Online publication date: 24-Mar-2005

An evidence-based approach to understanding the pharmacological class effect in the management of prostatic diseases
Christopher P. Evans, Neil Fleshner, John M. Fitzpatrick, Alexander R. Zlotta
Online publication date: 24-Mar-2005

Urological Oncology

Radical prostatectomy for clinically advanced (cT3) prostate cancer since the advent of prostate-specific antigen testing: 15-year outcome
John F. Ward, Jeffrey M. Slezak, Michael L. Blute, Erik J. Bergstralh, Horst Zincke
Online publication date: 24-Mar-2005

The influence of bladder neck mucosal eversion and early urinary extravasation on patient outcome after radical retropubic prostatectomy: a prospective controlled trial
Miguel Srougi, Mario Paranhos, Kátia M. Leite, Marcos Dall'oglio, Luciano Nesrallah
Online publication date: 24-Mar-2005

Prostate-specific antigen (PSA) complexed to α1-antichymotrypsin improves prostate cancer detection using total PSA in Japanese patients with total PSA levels of 2.0–4.0 ng/mL
Takashi Kobayashi, Toshiyuki Kamoto, Koji Nishizawa, Kenji Mitsumori, Keiji Ogura, Yoshihiro Ide
Online publication date: 24-Mar-2005

A novel technique for approaching the endopelvic fascia in retropubic radical prostatectomy, based on an anatomical study of fixed and fresh cadavers
Atsushi Takenaka, Ryoei Hara, Hideo Soga, Gen Murakami, Masato Fujisawa
Online publication date: 24-Mar-2005

The incidence and treatment of lymphoceles after radical retropubic prostatectomy
Ruth J. Pepper, Jhumur Pati, Amir V. Kaisary
Online publication date: 24-Mar-2005
776 Testosterone recovery and changes in bone mineral density after stopping long-term luteinizing hormone-releasing hormone analogue therapy in osteoporotic patients with prostate cancer

Robin Weston, Asad Hussain, Emmanuel George, Nigel J. Parr

Online publication date: 24-Mar-2005

780 Sexual, psychological and dyadic qualities of the prostate cancer 'couple'

Cynthia T. Soloway, Mark S. Soloway, Sandy S. Kim, Bruce R. Kava

Online publication date: 24-Mar-2005

786 Correlation between clinical and pathological staging in a series of radical cystectomies for bladder carcinoma

Vincenzo Ficarra, Orietta Dalpiaz, Najati Alrabi, Giacomo Novara, Antonio Galfano, Walter Artibani

Online publication date: 24-Mar-2005

791 A comparison of the pathology of transitional cell carcinoma of the bladder and upper urinary tract

Grant D. Stewart, Simon V. Bariol, Ken M. Grigor, David A. Tolley, S. Alan McNeill

Online publication date: 24-Mar-2005

794 The assessment of patient life-expectancy: how accurate are urologists and oncologists?

James R.M. Wilson, Michael G. Clarke, Paul Ewings, John D. Graham, Ruairidh MacDonagh

Online publication date: 24-Mar-2005

804 The pharmacokinetics of 400 µg of oral desmopressin in elderly patients with nocturia, and the correlation between the absorption of desmopressin and clinical effect

Gitte M. Hvistendahl, Anders Riis, Jens P. Nørgaard, Jens C. Djurhuus

Online publication date: 24-Mar-2005
Self-assessed health, sadness and happiness in relation to the total burden of symptoms from the lower urinary tract

Gabriella Engström, Lars Henningssohn, Gunnar Steineck, Jerzy Leppard

Online publication date: 24-Mar-2005

Nocturia in relation to somatic health, mental health and pain in adult men and women

Ragnar Asplund, Sven-Unno Marnetoft, John Selander, Bengt Åkerström

Online publication date: 24-Mar-2005

Nocturia, depression and antidepressant medication

Ragnar Asplund, Susanne Johansson, Svante Henriksson, Göran Isacsson

Online publication date: 24-Mar-2005

Combined external urethral bulking and artificial urinary sphincter for urethral atrophy and stress urinary incontinence

Nadeem U. Rahman, Thomas X. Minor, Donna Deng, Tom F. Lue

Online publication date: 24-Mar-2005

Day-case sling surgery for stress urinary incontinence: feasibility and safety

Subhasis K. Giri, John Drumm, Jean A. Saunders, Jane McDonald, Hugh D. Flood

Online publication date: 24-Mar-2005

A stereological analysis of fibrosis and inflammatory reaction induced by four different synthetic slings

Marcelo Thiel, Paulo C. Rodrigues Palma, Cássio L.Z. Riccetto, Miriam Dambros, Nelson R. Netto Jr

Online publication date: 24-Mar-2005

Sacral magnetic stimulation in non-inflammatory chronic pelvic pain syndrome

Thomas Leippold, Raeto T. Strebel, Mirjam Huwyler, Hubert A. John, D. Hauri, Daniel M. Schmid

Online publication date: 24-Mar-2005
Use of combined intracorporal injection and a phosphodiesterase-5 inhibitor therapy for men with a suboptimal response to sildenafil and/or vardenafil monotherapy after radical retropubic prostatectomy

Jack H. Mydlo, Rosalia Viterbo, Paul Crispen

The effect on erectile function of $^{103}$palladium implantation for localized prostate cancer

Anton Ponholzer, Renée Oismüller, Canatay Somay, Felix Büchler, Ulrich Maier, Robert Hawliczek, Michael Rauchenwald, Stephan Madersbacher

Comparison of laparoscopic and open donor nephrectomy: a randomized controlled trial

Nasser Simforoosh, Abbas Basiri, Ali Tabibi, Nasser Shakhssalim, Seyed M.M. Hosseini Moghaddam

Determination of the time required for appropriate chemical de-epithelialization of an ileal segment for cystoplasty: an animal model

Jalal Bakhtiari, Hamid Reza Fattahian, Mohammad Javad Gharagozlou, Abdolmohammad Kajbafzadeh, Seyed Reza Jafarzadeh

The laparoscopic management of intersex patients: the preferred approach

Francisco T. Dénes, Marcelo A.S. Cocuzza, Edison D. Schneider-Monteiro, Frederico A.Q. Silva, Elaine M.F. Costa, Berenice B. Mendonca, Sami Arap
Predictive factors of ultrasonographic involution of prenatally detected multicystic dysplastic kidney

Eli Armando S. Rabelo, Eduardo A. Oliveira, Guilherme Souza Silva, Isabela Leite Pezzuti, Edson Samesina Tatsuo

Online publication date: 24-Mar-2005

The promise of gene-expression analysis in bladder cancer: a clinician's guide

Steven C. Smith, Gary Oxford, Dan Theodorescu

Online publication date: 24-Mar-2005

Synergistic inhibitory effect of high-intensity focused ultrasound combined with chemotherapy on Dunning adenocarcinoma

Philippe Paparel, Laura Curiel, Sabrina Chesnais, Rene Ecochard, Jean-Yves Chapelon, Albert Gelet

Online publication date: 24-Mar-2005

Stereotactic electrical stimulation of the pontine micturition centre in the pig

Asger L. Dalmose, Carsten R. Bjarkam, Jens Christian Djurhuus

Online publication date: 24-Mar-2005

Gene transfer of vasoactive intestinal polypeptide into the penis improves erectile response in the diabetic rat

Zhou-Jun Shen, Hua Wang, Ying-Li Lu, Xie-Lai Zhou, Shan-Wen Chen, Zhao-Dian Chen

Online publication date: 24-Mar-2005

Assessment of microheterogeneity of blood flow in the rat urinary bladder by high-resolution digital radiography

Takahiro Kimura, Tokunori Yamamoto, Atsushi Sone, Atsushi Takenaka, Masato Fujisawa

Online publication date: 24-Mar-2005
Pharmaceutical review

899 Back to the future for urological drug development?

Michael G. Wyllie

Online publication date: 24-Mar-2005

Points of Technique

901 Modified tubularized transverse preputial island flap repair for severe proximal hypospadias

Rakesh P. Patel, Aseem R. Shukla, J. Christopher Austin, Douglas A. Canning

Online publication date: 24-Mar-2005

905 Tubeless and stentless percutaneous nephrolithotomy

Vikas Gupta, Trilok C. Sadasukhi, Krishan K. Sharma, Ram G. Yadav, Rajeev Mathur

Online publication date: 24-Mar-2005

Letters

907 The molecular staging of prostate cancer

George Yardy, Stephen McGregor, Walter Bodmer

Online publication date: 24-Mar-2005

907 Prostate size influences the outcome after presenting with acute urinary retention

Alan McNeill

Online publication date: 24-Mar-2005

908 Robotically assisted surgery

Christopher G. Eden

Online publication date: 24-Mar-2005

09 Prostate cancers in the transition zone: Part 2; clinical aspects

Joe Philip, Ramaswamy Manikandan

Online publication date: 24-Mar-2005
909 Comparative study of dartos fascia and tunica vaginalis pedicle wrap for the tubularized incised plate in primary hypospadias repair

Vemuri V.S.S. Chandrasekharam

Online publication date: 24-Mar-2005

909 Sacral ratio and fecal continence in children with anorectal malformation

Suzi Demirbag, Emre Senel, Salih Cetinkursun

Online publication date: 24-Mar-2005

Surgery Illustrated

911 Radical retropubic prostatectomy: apical preparation and curtain dissection of the neurovascular bundle

Wolfgang Horninger, Hannes Strasser, Georg Bartsch

Online publication date: 24-Mar-2005

924 Erratum

Online publication date: 24-Mar-2005

925 Abbreviations

Online publication date: 24-Mar-2005

926 Diary

Online publication date: 24-Mar-2005
The Fourth International Symposium on Genitourinary Cancers was an excellent meeting, with presentations from many leading medical and radiation oncologists, as well as from a handful of urologists.

Although there are many areas in the treatment of urological cancer in which the interests of urologists and medical or radiation oncologists meet, it is selectively uncommon that urologists attend oncology meetings, or indeed that oncologists attend urological meetings. I believe that we need to have a greater understanding of each other’s approach to patient care, and this can only come from greater dialogue between the groups, which will inevitably lead to improvements for patients. The multidisciplinary team approach now adopted by most urology departments has been a great advance in this regard, but this must surely lead logically to more widespread attendance at each other’s academic meetings and conferences.

To ‘test the water’, I attended the Fourth International Symposium on Genitourinary Cancers, held in Los Angeles, and organised by Nick Vogelzang, Cora Sternberg, Arie Belldegrun and Richard Cote. This was an excellent meeting, with presentations from many leading medical and radiation oncologists, as well as from a handful of urologists. The opportunity to hear the latest pharmaceutical management of advanced urological cancer was most welcome, and I feel that the input from the urologists present was also well received. There are many very large oncology meetings, such as ASCO and AACR, which many of us attend, but this smaller-scale meeting allowed considerable time for friendly discussion and informal interaction between the groups which might not have been possible at larger meetings. The Fifth Multidisciplinary Symposium on Genitourinary Cancers is scheduled to be held in Los Angeles in January 2006, and should be attended by urologists interested in urological cancer.

From the point of view of the BJU International, I am pleased to say that many papers from the above meeting will appear in print in the forthcoming months, showing our dedication to serving the diversity of the urological community.

I have decided to stop publishing Points of Technique in the BJU International; this is something that myself and the Editorial Team have been considering for some time, and I feel that it is now the right time to change our policy on publishing these types of papers. There are several Points of Technique already accepted and awaiting publication, so they will continue to appear in print for the next few months before they disappear. However from this month I would ask that they be no longer submitted for consideration.

JOHN M. FITZPATRICK
Editor-in-Chief
INTRODUCTION

Urological surgery has embraced the use of robotics since the late 1980s, when Guy’s Hospital and Imperial College London collaborated on clinical trials of a robotic TURP frame [1]. Following this pioneering experience by Wickham and colleagues, further developments in robotic urology moved to the USA and mainland Europe. This is possibly not only a result of surgical scepticism and lack of vision, but also the prohibitive initial expense of establishing a robotic programme. In an institution such as the UK National Health Service, free at the point of delivery, funding for a technological innovation such as robotic surgery has a lower priority than, e.g. stroke rehabilitation or diabetes, and rightly so. New technology does not necessarily produce durable results 5–10 years later. Each development must be supported by evidence showing it to be more effective than traditional open surgery. Robotic radical prostatectomy has previously been performed in the UK but results in a trial with many patients are lacking. As evidence of its efficacy and that of other robotic procedures emerges from the Vatikutti Institute [2,3] there is increasing interest in robotic urology amongst British urologists, many of whom enthusiastically participated in the first UK robotic urology symposium at Guy’s in 2004. Establishing a structured robotic urology programme involved five key steps: funding, basic science, training, clinical experience and evaluation.

FUNDING

Funding for the Da Vinci™ robotic system (Innovative Surgical, Sunnyvale, CA) was obtained as a competitive project grant from the Charitable Foundation of Guy’s and St. Thomas’. This grant was not intended only to purchase the robot and maintain it, but also for its scientific evaluation. Before this, funding for an AESOP voice-controlled robotic arm and transatlantic telerobotic trials using the RCM-PAKY robot came from the Guy’s Hospital Trust, the Guy’s and Johns Hopkins urology research funds, and the Friends of Guy’s.

INVESTING >£1 million in clinical robotics needed prior evidence of the effectiveness of robotics in a laboratory. To our knowledge the only randomized, controlled trial of robotics in urology was the recent transatlantic study between Guy’s and Johns Hopkins. Statistical analysis with adequate power required a total of 304 telerobotic percutaneous nephrolithotomies, which could not be ethically supported in humans and was legally unacceptable in animals in the UK. A specially designed and validated kidney model was used (Limbs and Things, Bristol, UK) and either a robotic arm (152 procedures) or a urologist (152 procedures) inserted a percutaneous needle. Thirty remote procedures were performed from Baltimore via four ISDN lines. The trial showed the robot to be slower but more accurate than humans. All urologists made fewer needle passes while using the robotic arm. A crossover trial subsequently showed that the robot can be controlled equally well from the UK to the USA as it is in the opposite direction [4].

Training

The robotics group, including surgeons and nurses, were initially trained on a Da Vinci ‘dry-lab’ and subsequently a ‘cadaveric lab’ in Paris. They then travelled to the Vatikutti Institute in Detroit to observe robotic urology in a high-throughput unit. An experienced robotic urologist (A.K.H.) from the same institute mentored the initial UK operations.

Clinical Experience: The First Four Cases

Permission to commence clinical robotics with the Da Vinci system was obtained by formal applications to the local clinical governance committee, which reports to the National Institute of Clinical Excellence. Patients were counselled about the operations by surgeons and a robotics nurse, particularly that they were new procedures at our centre. They were given information leaflets and shown a generic video of the Da Vinci robot in action.

The mean (range) docking time (the time taken to attach the robot to the patient) was 7 (5–9) min. Robotic radical prostatectomy (bilateral nerve-sparing) and robotic cystectomy (unilateral nerve-sparing on the side contralateral to the tumour in men) were performed using a six-port transperitoneal technique. Ileal conduit diversion after cystectomy/anterior exenteration for bladder cancer was performed through a 4–5 cm incision for delivering the bladder and lymph nodes in laparoscopic sacks. Robotic
colposuspension was performed by a four-port extraperitoneal technique. None of the patients needed a blood transfusion, which is particularly encouraging after cystectomy. The details are shown in Table 1.

**EVALUATION**

To establish its place in urology robotics requires a rigorous scientific evaluation. A ‘Evaluation Steering Group’, including clinicians and scientists with expertise in the area, has been set up to oversee this process. The effects of robotic surgery on operative times, pain control, oncological outcome and full recovery are being assessed prospectively in a pilot study. Robotics will then be compared to traditional open surgery and pure laparoscopy, ideally in a randomized controlled trial. Validated patient-satisfaction surveys, quality-of-life questionnaires and disability scales are being used to obtain objective data. The effect of robotics on hospital stay, waiting times and overall quality of service is being assessed. A health-economic evaluation will specifically assess resource inputs and cost-benefit analysis. The ergonomics of robotic urology will be compared to laparoscopic and open surgical techniques. Analytical evaluation of robotic movements and stereoscopic vision is in progress. This was first developed for space robotics and uses performance-to-resource ratios [6].

**THE FUTURE**

There has been much progress since the initial enthusiasm for urological robotics [6]. A structured project in urological robotics has been established in the UK. Urological robotics has a bright future, and deserves rigorous scientific evaluation. It may be possible for master-slave systems to be adapted to work with a virtual-reality training system. It will be possible for most surgeons to learn from previous errors by repeating key parts of the operation in a virtual environment [7]. Image guidance can help in this, as well as during the surgical procedure in real time.

**ACKNOWLEDGEMENTS**


**REFERENCES**


2 Tewari A, Srivasatava A, Menon M and members of the VIP Team. A prospective comparison of radical retropubic and robot-assisted prostatectomy: experience in one institution. BJU Int 2003; 92: 205–10

3 Menon M, Hemal AK, Tewari A et al.

**LAPAROSCOPIC RECONSTRUCTIVE UROLOGY**

SRAVANTI P. TEGAVARUPU and PROKAR DASGUPTA — Department of Urology, Guy’s and St. Thomas’ Hospitals and GKT School of Medicine, London, UK

Accepted for publication 26 October 2004

**KEYWORDS**

reconstruction, laparoscopy, robotics

**INTRODUCTION**

Over the last few years, the applications of laparoscopic surgery have been widely extended from diagnostic to most therapeutic ablative procedures, and of late to reconstructive surgery. There is emerging evidence to show that laparoscopic reconstructive procedures are at least as effective as traditional open surgery but with lower morbidity.

TABLE 1 The initial UK experience with the Da Vinci robotic system

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Sex</th>
<th>Time, min</th>
<th>Blood loss, mL</th>
<th>Early outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radical prostatectomy</td>
<td>M</td>
<td>185</td>
<td>300</td>
<td>Gleason 3 + 3; margins –ve</td>
</tr>
<tr>
<td>Radical cystectomy</td>
<td>M</td>
<td>340</td>
<td>150</td>
<td>G3T4a; TCC; margins –ve</td>
</tr>
<tr>
<td>Anterior exenteration</td>
<td>F</td>
<td>295</td>
<td>100</td>
<td>Extensive OIS; margins –ve</td>
</tr>
<tr>
<td>Colposuspension</td>
<td>F</td>
<td>140</td>
<td>20</td>
<td>Continent</td>
</tr>
</tbody>
</table>

Nerve-sparing robot assisted radical cystoprostatectomy and urinary diversion. BJU Int 2003; 92: 232–6


7 Nedas TG, Challacombe B, Dasgupta P. Virtual reality in urology. BJU Int 2004; 94: 255–7

Correspondence: Prokar Dasgupta, Department of Urology, 1st Floor Thomas Guy House, Guy’s Hospital, London SE1 9RT, UK. e-mail: prokar.dasgupta@gstt.sthames.nhs.uk

© 2005 BJU INTERNATIONAL
COMMENTS

FIG. 1. The current status of the various procedures in laparoscopic reconstructive urology.

Laparoscopic reconstructive procedures

**Upper tract**
- Pyeloplasty
- Ureterolithotomy

**Developing**
- Partial adrenalectomy
- Partial nephrectomy
- Nephropexy
- Pyelolithotomy

**Established**
- Calyceal diverticulectomy
- Ureteroureterostomy
- Ureteric reimplantation

**Miscellaneous**
- Orchidopexy
- Sacrocolpopexy

**Lower tract**
- Bladder neck suspension
- Radical prostatectomy
- Cystectomy
- Bladder augmentation
- Vesicovaginal fistula repair
- Sacrocolpopexy
- Pyelolithotomy
- Ureterolithotomy

The results of laparoscopic colposuspension are more controversial and its effectiveness was evaluated in a recent systematic review of five trials comparing laparoscopic to open colposuspension. Subjective cure rates at up to 18 months of follow-up were comparable (85–100%), while blood loss and hospital stay were shorter in the laparoscopic group [4]. Long-term follow-up and randomized trials to assess the durability of laparoscopic colposuspension are necessary.

Guillonneau et al. [5] popularized laparoscopic radical prostatectomy (LRP) and reported equivalent outcomes to open surgery (ORP), with excellent operating times and minimal blood loss. LRP can be performed both trans- and extraperitoneally, and the urethrovaginal anastomosis is completed either by interrupted or running intracorporeal sutures. RP is increasingly being performed robotically; in their unrandomized comparison of 200 robotic RPs with 100 ORPs, the Detroit team reported similar operative times, and none of the patients needed a blood transfusion after robotic RP, compared with 67% of the open group. In their single-centre experience the hospital stay was 1.2 days for robotic, 1.3 days for LRP and 3.5 days for ORP; the respective catheter duration was 7, 8 and 15 days, although with a continuous suturing technique of urethrovaginal anastomosis the catheter duration after robotic RP has reduced to 4 days [6], which is similar to LRP in other centres [5]. Experienced open surgeons have also tried to reduce the catheter duration to 7 days in ~75% of their patients, although this is still longer than that reported after LRP and robotic RP. In Detroit, positive margins were more frequent after ORP, at 23% for open and 9% for robotic surgery. In comparison, expert open and laparoscopic [5] surgeons have reported positive surgical margins of 12.8% and 13.7%, respectively.

The laparoscopic approach to cryptorchidism traditionally consisted of the diagnostic evaluation of the impalpable testis. Laparoscopic and needle-scopic one- and two-stage orchidopexy have shown complete success rates with almost no complications [1]. Experienced surgeons are performing laparoscopic partial adrenalectomy and nephrectomy. At present the complication rates of laparoscopic partial nephrectomy are somewhat higher than its open counterpart, but with increasing experience and better ways of achieving haemostasis it is likely that the results will become equivalent. Other laparoscopic reconstructive procedures include bladder augmentation, nephropexy, vesicovaginal fistula repair, sacrocolpopexy, renal artery aneurysm repair and urethral sling insertion (Fig. 1).

Laparoscopic pyelolithotomy, sometimes combined with pyeloplasty [2] and ureterolithotomy, have been successful in patients after failed ESWL or ureteroscopic manipulation. Two cases of laparoscopic ureterocalycostomy have been reported with successful outcomes after failed pyeloplasty [7]. Laparoscopic ileal ureter and ureteric reimplantation are still developing.

Laparoscopic cystectomy and urinary diversion is becoming popular because of the significantly lower blood loss and hospital stay. It is an advanced procedure and early outcomes indicate oncological equivalence to open cystectomy [8]. Laparoscopic ileal conduit and orthotopic neobladder construction are developing but are time-consuming; thus most surgeons currently create a laparoscopically assisted ileal conduit through small muscle-splitting or midline incisions. In an animal study, the formation of an ileal conduit and orthotopic neobladder by complete intracorporeal techniques took ~2.5 and 4.5 h, respectively [9]. With increasing experience it is anticipated that these operative times will improve.
CONCLUSION

Laparoscopic reconstructive urology is technically feasible but challenging. The major limitations are prolonged operating times, limited instrumentation, small working spaces and fixed angles at the trocar level to place sutures. Robotic assistance has provided increased dexterity because of the intuitive motion, and may overcome these technical difficulties. Larger series with a meticulous follow-up are required to determine the place of many of these developing laparoscopic reconstructive procedures.

ACKNOWLEDGEMENTS

We thank the Guy’s and St. Thomas’ Charitable Foundation, Geoff Koffman, Abhay Rane and Peter Rimington.

REFERENCES

6 Menon M, Hemal AK, Tewari A, Shrivastava A, Bhandari A. The technique of apical dissection of the prostate and urethrovescical anastomosis in robotic radical prostatectomy. BJU Int 2004; 93: 715–9
8 Rimington P, Dasgupta P. Laparoscopic and robotic radical cystectomy. BJU Int 2004; 93: 460–1

Correspondence: Prokar Dasgupta, Department of Urology, 1st Floor Thomas Guy House, Guy’s Hospital, London SE1 9RT, UK. e-mail: prokar.dasgupta@gstt.soton.nhs.uk

Abbreviations: L(0)RP, laparoscopic (open) radical prostatectomy.

INTRODUCTION

Urology has a reputation for promoting advances in technology; the development of ESWL, sophisticated minimally invasive procedures and advances in robotic surgery are a testament to urological innovation. Naturally, in some fields of endeavour other medical specialists have been the pioneers. e.g. in cardiovascular disease, where the combined advances in engineering and interventional cardiology have lead to the development of drug-eluting devices such as coronary stents [1]. Urinary tract drainage by catheters and stents represents a fundamental aspect of urological practice. The time is ripe to evaluate drug-eluting compounds for possible use in urological biomaterials.

THE PROBLEMS

Indwelling catheters and stents are plagued with three primary problems that limit their function, i.e. encrustation, infection and patient discomfort. All indwelling catheters and stents will eventually encrust. This can lead to UTIs, increased patient discomfort and difficulties with removal. Attempts have been made to develop devices that resist encrustation but none have eliminated the problem completely. Currently, treatment with antibiotics and analgesics is only a temporizing measure; removing the device is the only definitive solution.

Several experimental models are available to evaluate the problem of encrustation. These include ex vivo artificial urine models, animal models such as the pig or the rabbit, and human studies. The primary goal of most of the work to date is to develop a stent and/or catheter with long-term resistance to encrustation. This would limit the need for regularly changing the devices. In addition, decreased encrustation may reduce the number of UTIs that require antibiotic treatment. Heparin-coated ureteric stents were evaluated in a clinical study, which showed that after being in situ for up to 6 weeks, heparin-coated stents remained free of encrustation, as opposed to uncoated control stents which began to encrust within 14 days [2]. Another novel attempt at decreasing encrustation was to coat silicone disks with oxalate-degrading enzymes, produced by Oxalobacter formigenes. The disks were implanted into rabbit bladders and left in situ for 30 days. The disks coated with oxalate-degrading enzyme had less encrustation after 30 days than uncoated control disks [3]. This is a promising advance and paves the way for future clinical studies.

A SOLUTION

Reports from cardiology show that stents can be not only ‘coated’ with a drug, but that the drug can be loaded directly into the bulk material, thereby allowing it to elute in a controlled fashion over time [1]. Sticker et al. [4] reported that triclosan (an antimicrobial found in many products, ranging from mouthwash and toothpaste to children’s toys), in an artificial infected-urine model, could prevent biofilm formation and encrustation of Foley catheters. We evaluated triclosan-eluting stents in an infected-rabbit model [5]. Segments of stents were endoscopically placed into rabbit bladders that were infected with Proteus mirabilis. After 7 days, 7 of the 12 rabbits implanted with triclosan-eluting stents had cleared the P. mirabilis infection, vs none of 22 with control stents. Triclosan-eluting stents also

DRUG-ELUTING BIOMATERIALS IN UROLOGY: THE TIME IS RIPE

BODO E. KNUDSEN, BEN H. CHEW and JOHN D. DENSTEDT – Division of Urology, The University of Western Ontario, London, Ontario, Canada
had less adherent bacteria than controls. Many urologists routinely place patients on oral antibiotics after ureteric stenting. A triclosan-eluting stent may be able to reduce the need for oral antibiotics; human trials appear warranted.

LUTS secondary to indwelling catheters and stents remain a difficult problem. Numerous attempts have been made to decrease the discomfort of ureteric stents, e.g. duallumen stents and tail stents [6], but a definitive solution to improve patient comfort remains elusive. Drug-eluting stents may represent a breakthrough in attempts to modify stent symptoms. To evaluate which pharmaceuticals may be beneficial intravesically, to mimic a drug-eluting stent, a recent study evaluated the effect of an intravesical instillation with oxybutynin, ketorolac or lidocaine immediately after placing a ureteric stent in patients undergoing ESWL. Objective symptom scores showed that patients receiving ketorolac had significantly less flank pain at 1 h after the procedure. Moreover, all drugs were safe and there were no adverse effects [7]. This study should serve as the foundation for future studies of stent comfort to evaluate drug-eluting urinary stents.

There are many other potential applications for drug-eluting technology in urology. Currently patients are treated with weekly instillations of BCG for Ta and T1 urothelial cell cancers of the bladder. Theoretically it is possible that a continuous indwelling delivery method for BCG, or a chemotherapeutic agent such as mitomycin C, might provide both a more tolerable and perhaps more effective delivery system. Similarly, treating upper-tract urothelial cell cancers with BCG or chemotherapeutic agents has been cumbersome, requiring either a nephrostomy tube or reliance on reflux with a ureteric stent in place. Neither method ensures prolonged contact of the reagent with the cancer; a drug-eluting stent may provide such a solution.

Patients with interstitial cystitis remain some of the most challenging for the urologist to treat. Resiniferatoxin administered locally to the bladder continuously over 10 days via an infusion pump gave positive results in such patients [8]. A continuous local drug delivery via a drug-eluting biomaterial might provide long-term symptomatic relief in these difficult-to-treat patients.

Drug-eluting biomaterials applied to urology hold considerable promise. The potential to reduce encrustation and limit UIIs would be a significant breakthrough. The discomfort of urinary stents and catheters may be reduced by using drug-eluting biomaterials. Further expansion of the technology to treat other urological disorders also holds promise. Clearly, future studies are required to assess the safety and efficacy of these devices before this technology becomes incorporated into the standard of practice, but now is the time for urology to take a leading position in the development of drug-eluting biomaterials.

REFERENCES
4 Stickler DJ, Jones GL, Russell AD. Control of encrustation and blockage of Foley catheters. Lancet 2003; 361: 1435–7

Correspondence: John Denstedt, Department of Surgery, The University of Western Ontario, London Health Sciences Centre, 339 Windermere Road, London ON, Canada N6A 5A5.
e-mail: john.denstedt@sjhc.london.on.ca

THE EUROPEAN WORKING-TIME DIRECTIVE: ONE STEP FORWARD, TWO STEPS BACK – MAJID SHABBIR, PETER AMOROSO and ROGER S. KIRBY
– St George’s Hospital & The London Clinic, Harley Street, London, UK
Accepted for publication 26 November 2004

INTRODUCTION
We are now in a new era of medical practice; the UK has finally come into line with the rest of the Continent and the European Working Time Directive (EWTD), which was integrated into British law in 1998, has at last been extended to include the medical profession. This directive is essentially a Health and Safety law, aimed at reducing the working week to a maximum of 56 h by August 2004, and to 48 h by 2009. While no one can question the logic behind this law, concerns exist as to its effect on an already strained UK National Health Service (NHS). The changes needed to make hospitals compliant with the EWTD have seen the greatest overhaul of the NHS for some time. The effect of these changes will alter the way we teach and practice medicine, and the consequences of this law will resonate long into the future.

The greatest concerns with the implementation of the new working hours are the effects on training and the quality of clinical care. Medicine has traditionally been taught by a system of apprenticeship. Less time spent at work will undoubtedly result in reduced training opportunities. A report from the Royal College of Surgeons calculated that before the Calman report, the average junior doctor spent ≈ 30 000 h at work before becoming a consultant. With the new changes to the system this figure is set to fall to
6000–8000 h [1]. While no one wishes to go back to the ‘bad old days’ of 120-h working weeks, this dramatic change will lead to greater inexperience at the consultant grade. While surgical training has been refined to ensure that essential skills are adequately taught, nothing will account for the experience gained from high exposure to a wide variety of different conditions. In medicine not all cases are straightforward, and the ability to deal with unusual and often unpredictable situations is best enhanced with time.

As well as reducing the total hours worked, the EWTD also limits the total continuous hours worked to 13 in a 24-h period, with the definition of ‘work’ extended to include time in the workplace on-call, even if asleep. Most EWTD-compliant rotas work on a full-shift system, with weeks of night duty. Current hospital policy means that operations are only performed at night if the condition is life-threatening. This means that cases such as appendicectomy, which were the bread-and-butter of surgical training, are now rarely performed on-call. The admitting surgeon at night is also prevented from operating the next morning, as his continued presence at work contravenes the new directive. To add to the problem, the week of nights is usually followed by time off, which results in further lost opportunities with elective operating lists. A recent study highlighted this problem, showing that, on average, elective surgical experience was reduced by a third with directive-compliant full-shift rotas [2].

At present, the surgical trainee is under fire and already having to fight for adequate operative experience. The increase in staff-grade doctors and nurse specialists, both with an emphasis on increased provision of service, is diluting many training opportunities. In addition, the development of ‘treatment centres’ as part of the government’s waiting-list initiative is also removing the prospect of vital training [3]. With the additional problems that the EWTD brings, even more care must be taken to ensure that remaining compliant with the EWTD is not at the expense of developing competently trained consultants. This is of even greater importance in urology, which is now on the brink of a new phase, with a shortened training programme aimed at producing ‘office urologists’ within 3 years of specialist registrar training.

The other major area of concern with the EWTD is its potential effect on the quality of clinical care. Implementation of the new restrictions to the working week has led to fewer staff on duty at any given time and a subsequent increase in the development of cross-cover between specialties. This has three potential problems: (i) A worrying lack of specialist expertise available on-call; (ii) Breakdown in the continuity of patient care, with the admitting team often different from the team caring for the patient for the remaining admission. This increases the need for careful transfers and raises the possibility of potential error; (iii) Fewer staff on call leads to an over-stretched service and a greater possibility of problems being detected late, often when corrective measures may be ineffective.

This pressure cooker environment is a potential breeding ground for mistakes. In the present era of clinical governance, there is a moral and legal duty to ensure the delivery of high-quality clinical care. Should we forget, we are quickly reminded of the consequence of failure by the increasingly litigious environment in which we live and work. Changes are therefore essential to prevent the disintegration of the NHS, and the sooner the better.

Increasing the number of doctors provides a long-term solution to the reduction in working hours and the need to maintain a high standard of clinical care. The Department of Health has already realized this and planned expansion across the grades, with a 25% increase in the number of surgical consultants by 2004 (1100 posts), and a further proposed increase of 43% by 2010 [4]. However, this is still short of the 7000 new posts that the British Medical Association’s Junior Doctors’ Committee quoted in 2001 as being necessary to meet targets. Although expansion of numbers is a possible solution, the funding required to implement this strategy fully is not available at present, or indeed in the near future. Recruiting more doctors may therefore not be the most effective way of using available financial resources [5]. One potential solution, which is due to be implemented in urology, is the development of the ‘office urologist’ post. This may indeed be the way forward, particularly in a specialty where fewer patients require a definitive surgical procedure. The resultant increase in the number of consultants under this new scheme will improve service provision within the speciality, and improve patient waiting times. However, not all urologists welcome this new development with optimism; many feel that the new 3-year training programme will be too short to develop the necessary experience and responsibility required to become a consultant, with the potential need for continued mentorship forming an updated version of the old senior registrar post.

Despite the criticism, the proposed changes offer a possible solution to the EWTD at a time when options are otherwise limited. While teething troubles are to be expected at the start, the new system should improve patient care in the long term, although its effect on training is yet to be established.

The EWTD is here to stay. It is important that we take great care to ensure that its implementation does not risk the future of healthcare in the UK. The policies adopted now will shape the medical profession forever, and may well decide whether the NHS will sink or swim. Every effort must be made to ensure that training standards are maintained while trying to meet the pressures of service provision in the new restricted-hours system.

REFERENCES

5 MacDonald R. More doctors is not the answer to the European Working Time Directive. BMJ 2003; 326: 68

Correspondence: Majid Shabbir, Department of Urology, St George’s Hospital Cranmer Terrace, London SW17 0RE, UK.
e-mail: majidshabbir@hotmail.com
Peyronie's disease: the epidemiology, aetiology and clinical evaluation of deformity

CHRISTOPHER J. SMITH, CHELSEA MCMAHON and RIDWAN SHABSIGH
Department of Urology, Columbia University, New York, New York, USA
Accepted for publication 23 September 2004

KEYWORDS
Peyronie's disease, epidemiology, aetiology, clinical evaluation

DEFINITION
Peyronie's disease (PD) is a localized connective tissue disorder that affects the tunica albuginea of the penis. Fibrous scar tissue, which replaces the normally elastic fibres, causes a characteristic penile deformity that is most evident during erection. This pathological process can manifest as increased curvature, indentation, shortening or an 'hourglass' irregularity of the penis. The diagnosis of PD is often preceded by painful erections, and can be associated with erectile dysfunction and palpable areas of induration (plaques).

EPIDEMIOLOGY
While PD was once considered to be relatively uncommon, studies now suggest that its prevalence is similar to that of diabetes or urolithiasis [1]. A recent epidemiological study reported an overall prevalence of the condition of 3.2% [2], much higher than once thought, highlighting the potential physical and psychosocial impact of the disease on society. Compounding these effects on the community are the changing demographics of the population, which are predicted to increase age-related conditions.

AETIOLOGY AND PATHOPHYSIOLOGY
Of concern is the belief by some that even the most recent data underestimate the true prevalence of PD. Men might be reluctant to report a condition that they consider embarrassing, and older men might often accept their symptoms as insignificant consequences of ageing. Many physicians agree that the true prevalence of PD has become more apparent since the advent of oral sildenafil, which has seen a marked improvement in community awareness of erectile dysfunction [1].

Unfortunately, the quality of epidemiological data on PD remains erratic, with one contributing factor being the various criteria used by researchers to define the condition. The most accepted objective measures include the number, size and location of plaques, as well as induration and curvature. Nevertheless, epidemiological data have been used to propose risk factors associated with PD. Hypertension, smoking, diabetes and hyperlipidaemia have all been suggested as risk factors, but these are more likely to be related to erectile dysfunction in general, and current research has shown no substantial relationship between these factors and the severity of penile curvature [3].
(in vivo) and cell culture (in vitro) models have provided an invaluable medical platform to analyse the pathophysiology of PD. El-Sakka et al. [4] used rats as an experimental model in a causal in vivo investigation of PD. Injections of cytomodulin (a synthetic heptapeptide with a similar action to TGF-β) into the penile tissue of rats consistently produced an intense fibrotic reaction in the tunica albuginea. The study provided evidence of the pathogenetic function of TGF-β in PD, and promoted the use of in vivo analysis as an effective tool in the search for therapeutic solutions.

Mulhall et al. [5] cultured cells from plaque-derived tissue; this in vitro analysis showed reliable phenotypic, genotypic and functional alterations in pathologic tissue compared to normal tunica-derived or neonatal foreskin-derived fibroblasts. While this model was not able to flawlessly replicate the in vivo environment, it allowed an investigation of factors upstream of TGF-β that influence the pathogenetic pathway. Other advantages of the cell-culture model include cost and time efficiency, reproducibility, and the identification of tissue cell variance between patients.

Many of the theories that seek to explain the pathogenesis of PD have been derived from either animal or cell-culture research. While trauma is considered to be the provocative stimulus, other theories include: failure of fibrin clearance; collagen alterations; genetic predisposition; autoimmune factors; free radical production; and cytogenetic aberrations. In 2003 Mulhall [6] described a paradigm that encompassed these different theories to explain plaque developmental pathogenesis in PD; an adapted version follows:

- **Penile trauma in genetically susceptible males**, leading to;
- endogenous and/or exogenous factors (localized autoimmune response), leading to;
- loss of suppressor genes and activation of promoter genes, leading to;
- cyclin-cycle regulator dysfunction, leading to;
- biological transformation of constituent cells within tunica/plaque, leading to;
- cytokine over-expression, free radical production and cytogenetic changes, leading to;
- unregulated extracellular matrix deposition (fibrin and collagen), leading to;
- plaque formation.

**TRAUMA**

Trauma is reported to be the important initiating factor, and the ensuing inflammatory response is considered to be heightened through confinement in the densely packed layers of the tunica albuginea. It is proposed that the trauma originates from excessive physical forces inflicted on the penis during penetrative sex, which result in tunical delamination and microhaemorrhaging into the subtunical spaces [6]. The subsequent formation of scar tissue in the tunica albuginea occurs where the strands of the septum are attached to the dorsal and ventral aspects of the penis; these are the points under maximum stress when the elastic tissue of the penis is stretched to its capacity (7).

The fibrin deposited initially as a consequence of repetitive microvascular injury is a normal component of wound healing, but pathological scar tissue forms when repetitive trauma leads to inadequate resolution of the lesion [7]. Recent research has shown that the additional accumulation of collagen in the tunica albuginea is disorganized, and there is a diminished and chaotic dissemination of elastin fibres [8]. Despite these findings, more information is needed on the cause of the fibrin deposition and subsequent failure of degradation.

**GENETIC PREDISPOSITION AND AUTOIMMUNE FACTORS**

Genetic predisposition has been suggested as a causal factor, because of the familial clustering of the condition, and studies assessing human leukocyte antigen linkage have shown that PD is strongly associated with both Dupuytren’s contractures and human leukocyte antigen B27 [6]. Patients with PD have various degrees of autoimmunity, supporting the theory that an autoimmune reaction after trauma might be the cause of the additional fibrosis and scarring [9]. Diverse markers of immune incompetence were reported in affected patients, but the proposed autoimmune susceptibility is believed to be localized to the tunica albuginea.

**CYTOGENETIC ALTERATIONS**

Chromosomal instability has been shown in fibroblasts from pathological plaques in PD, and similar cytogenetic abnormalities have been found in samples from patients with Dupuytren’s contracture. This raises the possibility of a common pathway leading to fibrosis. Genotypic analyses have shown that chromosomal instability is significant in plaque-derived cells with fibroblasts from either foreskin or normal tunica [5].

Profibrotic or fibrogenic cytokines increase fibroblast collagen production and proliferation rates. While there are many families of fibrogenic cytokines, it has been established that TGF-β1 is up-regulated in PD [10]. TGF-β1 also stimulates the expression of the profibrotic cytokines, including monocyte chemoattractant protein 1 and connective tissue growth factor. Further contributing to this fibrogenic effect, increased levels of basic fibroblast growth factor in plaque-derived cell cultures cause an overproduction of extracellular matrix by fibroblasts [11].

Cellular over-proliferation in PD is associated with aberrant p53 function that allows damaged cells to pass through the cell cycle and proliferate. This abnormal pathway has been shown in plaque-derived fibroblasts and indicates an absence of cell-cycle checkpoints in these cells [12]. While a significant presence of p53 protein has been recognized in pathological plaque fibroblasts, relatively low levels were found in normal control samples [13].

**FREE RADICAL FORMATION**

Cellular antioxidants are reported to have a role in preventing plaque growth in PD; their ability to combat the effects of free radicals, including reactive oxygen species and reactive nitrogen intermediates, appears to be an important component in minimizing the proposed damage caused by oxidative stress [14]. However, therapeutic antioxidants (vitamin E and superoxide dismutase) have been used with mixed success, and given that many signalling pathways are poorly understood, further research is needed to determine the function of free radicals in calcification and plaque formation.

Smooth muscle cells and macrophages, among other cell types, produce inducible nitric oxide synthase when stimulated. When this enzyme is up-regulated, high levels of nitric oxide generate potent free radicals, which lead to oxidative stress and poor vasorelaxation. Although this process is thought to exist in PD, some studies suggest that nitric oxide might limit tunical scarring

© 2005 BJU International
and contraction by restricting myoblast proliferation [15].

OTHER CAUSES

PD is also associated with invasive procedures on the penis, e.g. radical retropubic prostatectomy, cystoscopy and urethral catheterization; genital or peritoneal trauma; urethritis; uric acidaemia; and lipoma [16]. Atherosclerosis has been mentioned as a specific area of interest, as its pathological mechanism is similar to that of PD [5], as atherosclerosis is also subject to cellular over-proliferation leading to fibrotic plaque formation.

CLINICAL EVALUATION OF THE DEFORMITY

The accurate clinical evaluation of penile deformity secondary to PD requires both subjective and objective measures (Table 1).

SUBJECTIVE MEASURES

The initial component of a subjective evaluation is often achieved using a questionnaire or clinical history to estimate the degree of deformity and its effects on the patient's quality of life. There are many established questionnaires to assess sexual function, including the International Index of Erectile Function, the Derogatis Interview for Sexual Functioning, and the Social Desirability Scale. The Peyronie's Disease Index, first introduced by Shabsigh et al. [17], is a questionnaire specifically designed to address issues most pertinent to patients with PD.

The aim of the initial evaluation is to provide information on the duration of disease, recalled injury and presenting symptoms (curvature, length, rigidity, softening, erection pain, coitus, girth and hinge). Ideally, information on psychological distress and level of satisfaction should be obtained, as well as potential risk factors for erectile dysfunction. Strategies to elicit the patient's assessment of curvature direction and degree of severity might include the use of visual analogue scales.

The next component of subjective evaluation involves a physical evaluation. Levine and Greenfield [18] recommend that the examination should start with a routine genitourinary assessment, which is then extended to involve an assessment of hands and feet for indications of systemic fibromatosis (e.g. Dupuytren's contracture). Other subjective information sometimes noted on physical examination includes 'eyeball' evaluations of penile curvature, penile length change and differences in erection capacity. Girth-related changes are most commonly reported by the patients, despite the recommended use of string or flexible rulers to measure it directly.

OBJECTIVE MEASURES

The objective evaluation of penile deformity in PD includes measurements of length, plaque characteristics (size and location), erectile capacity and curvature. There is currently no standardized approach for assessing penile length, but it is recommended to measure it dorsally from the base to the meatus while the penis is at full stretch [18]. It is hoped that this will minimize the potential effect of proximal penile fat and skin variability. Unfortunately, measurements of length obtained in the erectile state are difficult to reproduce.

While a reduction in plaque size has not been shown to correlate with improvements in other functional deformities, it is often reported as a target for treating PD [18]. Measuring the plaque size is difficult because of extensions through the septum and variability in thickness, with the use of callipers or rulers thought to offer the most practical solution. Ultrasonographic techniques are useful to verify the presence of any arterial or mixed vascular abnormalities, and can be used to identify distinguishing plaque features including size, hypo/hyper-echogenicity, calcification and tunical albuginea thickening [19]. MRI might provide additional information about local inflammation if required [20].

Erectile capacity or rigidity is often measured subjectively in standardized questionnaires, and this is important in assessing patient satisfaction and quality of life. However, objective measurements can also be obtained using penile duplex ultrasonography after administering a vasoactive penile injection. Other objective measurement options include nocturnal penile tumescence and rigidity monitoring, and cavernosometry, but these are poor predictors of sexually induced erections [18].

Penile curvature is recorded at the point of maximum erection, and measurement by protractor is reported to be the most reliable technique. However, assessing penile angulation is often inaccurate because of variability in penile rigidity at the time of evaluation. Vacuum-induced erection in the clinic contributes to this variability, as the erection obtained is often not representative of the patient's normal erection. Measurement of angulation from photographs has also been suggested to be inaccurate because of several inconsistencies [18].

| TABLE 1 A summary of the clinical evaluation of penile deformity in PD |
|------------------------|------------------------|
| Measures | Subjective | Objective |
| Questionnaire or clinical history: | Penile length: | Measure dorsally from base to meatus |
| Presenting symptoms | Ensure penis is at full stretch |
| Duration of disease | Plaque characteristics: |
| Previous penile injury | Callipers or rulers most reliable |
| Risk factors for erectile dysfunction | Ultrasonography or MRI |
| Medical and sexual history | Erectile capacity: |
| Level of satisfaction | Penile duplex ultrasonography after a vasoactive penile injection |
| Psychological distress | Penile curvature: |
| Patient observations: | Protractor most reliable, recorded at point of maximum erection |
| Curvature direction and degree of severity | |
| Girth-related changes | |
| Physical examination: | |
| Genitourinary assessment | |
| Hands and feet for systemic fibromatosis | |
| 'Eyeball' curvature, length, and erection capacity | |

© 2005 BJU INTERNATIONAL
CONCLUSION

The prevalence of PD is much greater than previously thought, with the condition now reported to affect 3.2% of the male population. This confirms fears that it is becoming a major public health issue for ageing men, with action now required to minimize the impact on society. The development of extensive screening programmes would offer a means for evaluating associated comorbidities, and would provide a better understanding of the risk factors for PD. The need for medical practitioners to adopt a standardized approach to the clinical evaluation of penile deformity will also be greater as the condition becomes more common.

Much debate remains over the pathophysiological mechanisms leading to excessive scarring and fibrosis. Recent refinements of cell culture and animal models have enhanced understanding of what is thought to be a multifactorial process. While it appears that penile trauma is the major inciting factor in the causes of PD, it is unlikely to be solely responsible, as only some men are susceptible, despite having similar sexual experiences to the rest of the population. With further research into the pathological cascade of cellular and molecular events, and an increase in community awareness of the disease, the development of effective therapeutic and prophylactic measures will become a realistic objective.

CONFLICT OF INTEREST

None declared.

REFERENCES

20 Hauck EW, Hackstein N, Vossenrich R et al. Diagnostic value of magnetic resonance imaging in Peyronie’s disease: a comparison both with palpation and ultrasound in the evaluation of plaque formation. Eur Urol 2003; 43: 293–300

Correspondence: Ridwan Shabsigh, Department of Urology, Columbia University, New York, New York, USA.

e-mail: RShabsigh@urology.columbia.edu

Abbreviations: PD, Peyronie’s disease.
Recent advances in understanding the biology of diabetes-associated bladder complications and novel therapy

NAOKI YOSHIMURA, MICHAEL B. CHANCELLOR*, KARL-ERIK ANDERSSON† and GEORGE J. CHRIST‡

Departments of Urology and Pharmacology, *Urology and McGowan Institute of Regenerative Medicine, University of Pittsburgh, Pittsburgh, PA, †Department of Clinical and Experimental Pharmacology, Lund University Hospital, Lund, Sweden, and ‡Department of Regenerative Medicine, Wake Forest University, Winston-Salem, NC, USA

Accepted for publication 12 October 2004

INTRODUCTION

Diabetes mellitus (DM) is at epidemic proportions and becoming a major problem in the USA. According to the Centers for Disease Control and Prevention, 18 million people in the USA have DM and the prevalence of DM increased from 4.9% in 1990 to 7.3% in 2000 [1]. Urological complications have increasingly become a concern in those affected by DM (both Type I and II). More than a quarter of diabetic patients will develop costly and debilitating urological complications, e.g. incontinence, infections, loss of sensation and retention of urine. The total annual cost of diabetes in 1997 has been estimated at more than $98 billion (http://www.diabetes.org).

In addition to diabetic bladder dysfunction, there is a greater incidence of asymptomatic and symptomatic bacteriuria, which can progress to kidney infection and kidney damage. This increase in infection has been attributed to numerous causes, from incomplete bladder emptying to changes in bladder wall components and immune dysfunction. A confounding factor for all basic studies on the bladder is the lack of published data on the urothelial cell, vascular, neurological and smooth muscle function, and interactions in bladder tissue from nondiabetic sources that can be used for comparison with the diabetic.

An important question is whether bladder dysfunction is secondary to an inherent neuropathology induced by diabetes, or caused by changes associated with bladder overdistension. Many animal models have been used to elucidate this and other questions associated with diabetic cystopathy. Streptozotocin (STZ)-induced diabetic rats and sucrose-drinking rats (sucrose induces a polyuria similar to that seen in diabetic patients) have generally been used. Paro et al. [2] noted that alloxan-induced diabetic rats had decreased and irregular contractions, while sucrose-fed rats had normal bladder contractions. This suggests that in alloxan-induced DM, contractile dysfunction is secondary to an inherent diabetic cystopathy, while bladder hypertrophy in sucrose-fed rats is an organ adaptation to polyuria. Other differences between STZ-induced diabetes and sucrose-induced bladder distension include a decrease in noradrenaline uptake and in choline acetyltransferase activity [3], and cystometrographic and supraspinal reflex latencies between the groups [4].

Clinically, the diagnosis of diabetic cystopathy is most readily made with urodynamic testing [5,6]. The most common urodynamic findings include elevated residual urine volume, impaired bladder sensation, involuntary detrusor contractions, increased cystometric capacity and decreased bladder contractility. Cystometry may show detrusor areflexia, which is usually found in patients with an impaired sensation of bladder filling [7–9]. Detrusor overactivity is also common in patients with DM [10]. Other aspects of the severity of DM, e.g. duration, glycaemic control and microvascular complications resulting in damage to innervation of the bladder, have been suggested as possible mechanisms for incontinence [11,12].

PATHOPHYSIOLOGY

The biology of DM-associated bladder complications is multifactorial and they can be a result of an alteration in the physiology of the detrusor smooth muscle cell, the innervation or function of the neuronal component, or urothelial dysfunction (Fig. 1). The experimental model most often used to assess bladder complications is the STZ rat model. As bladder smooth muscle contraction is mediated by acetylcholine released by the pelvic nerve acting on muscarinic receptors, a series of pharmacological studies have focused on the impact of STZ-DM on the responsiveness of bladder strips to externally applied muscarinic agonists. Neuronal dysfunction may reflect a deficiency of axonal transport of nerve growth factor (NGF) and be important in inducing diabetic neuropathy [13–15]. The urothelium undergoes changes in DM; thus, in the STZ-induced DM rat model, there are progressive increases in total bladder tissue, with hypertrophy of the bladder wall and dilatation of the bladder [16,17]. Both smooth muscle and urothelium have been shown to increase significantly with time. Thus there is strong evidence that DM adversely affects the bladder smooth muscle, nerves and the urothelium (Fig. 1).

DM AND DETRUSOR SMOOTH MUSCLE FUNCTION

DM has been shown to alter detrusor smooth muscle function in experimental animals, with the vast majority of these studies conducted on the STZ rat model. However, because there are no longitudinal studies conducted under similar experimental conditions, there is still uncertainty about the time course, magnitude and mechanism of DM-related changes in detrusor smooth muscle cell function.

STZ-DM: Pharmacological studies on isolated bladder strips have generated much confusion. While there are generally changes in isolated detrusor smooth muscle cell strips
there is no agreement on either the phenomenon or the mechanism. For example, several studies documented an increase in responsiveness of DM bladder strips to externally applied muscarinic agonists [17,18] but others reported a decrease or no change in the muscarinic component [19]. There was an increase in muscarinic receptor density at both 2 and 8 weeks after STZ-induced DM [20]. A recent study found an increase in the β1-receptor-mediated relaxation response in isolated detrusor smooth muscle strips from 8–10 week STZ-DM rats [21]. Moreover, there was an increased contractile response to 5-hydroxytryptamine from 4-week STZ-DM rats.

One DM-related change that most experts agree on is an increased responsiveness of isolated rat bladder strips to electrical field stimulation (EFS) [22,23]. However, there is no consensus on the putative mechanism for this increased responsiveness to EFS. Theories include that the increased response to EFS is caused by DM-related changes in membrane lipid composition or other destabilizing membrane changes, or increased neurotransmitter release [24]. Belis et al. [25] suggested that the changes are related to increased calcium-channel activity, while Waring and Wendt [23] found no evidence for altered calcium regulation, and therefore suggested that the increased responsiveness may be a result of enhanced calcium sensitivity. Most recently, Bezuijen et al. [26] reported that decreased function was more notable in strips from diabetic rats with enlarged bladders. This does not elucidate the mechanism, but could explain some of the observed variability from previous studies. In addition, this same group recently showed that DM increases the rate of development of at least some aspects of bladder decompensation in rats with partial urethral outlet obstruction [27]. Such observations further highlight the multifactorial nature of diabetic cystopathy, and the potential array of causal mechanisms and clinical symptoms that might be apparent in an ageing population.

Hashitani and Suzuki [28] found increased depolarization of myocytes in STZ-DM rat bladder strips on applying acetylcholine, indicating enhanced muscarinic sensitivity in the diabetic bladder. They further noted decreased spontaneous electrical activity in the myocytes, presumably related to altered purinergic transmission. These observations are consistent with the effects generally associated with a decrease in neuronal transmitter release.

Poladia and Bauer [29] studied the changes in nitric oxide synthase (NOS) and reactive nitrogen species formation during DM-related bladder remodelling, using the STZ-DM rat model. They found early, time-dependent and cell-specific changes in the three isoforms of NOS, and region-specific increases in protein nitration. Endothelial NOS was significantly up-regulated in the lamina propria, neuronal NOS in the urothelium, lamina propria and in the smooth muscle layer, whereas inducible NOS was up-regulated only in the urothelium. They suggested that changes in NO production and impaired NO control are early events in diabetic cystopathy, and that mechanisms leading to increased oxidative stress and proteasomal activation may be key participants leading to organ dysfunction.

**BB/W rat**: There are only a few published studies with the BB/W rat diabetic model [14,22]. As with the STZ-rat model, the diabetic BB/W rat has the expected in vivo phenotypic characteristics, e.g. decreased overall body weight, and corresponding increases in voiding volumes and voiding frequency. From a mechanistic standpoint, Longhurst [30] reported an apparent absence of detectable effects of 6 months of DM in the BB/W rat on the pharmacology of isolated detrusor (i.e. bladder body) strip contractions. However, there were modest but statistically significant decreases in the sensitivity and magnitude of carbachol and ATP-induced contractions of detrusor strips when the data were normalized for tissue weight.

Given that motility disorders are an important component of diabetic cystopathy, it will be critical to more precisely determine the nature, time course, magnitude and mechanism for these changes (Fig. 2). Elucidating the contribution of detrusor myocytes to diabetic bladder disease will be important to the improved understanding, diagnosis and treatment of diabetic cystopathy. To do so will require multidisciplinary longitudinal studies in both man and experimental animals, in which the extent of DM is well characterized, and the effects of DM on bladder function in vivo documented.

**NEURONAL DYSFUNCTION IN DM**

Although the pathogenesis of diabetic neuropathy is not fully clarified, it is generally accepted that the cause of diabetic neuropathy is multifocal. Some of the
proposals for pathogenesis include altered metabolism of glucose, ischaemia, superoxide-induced free-radical formation and impaired axonal transport [31]. It is also known that the neuropathies of DM caused by the metabolic derangement of the Schwann cell result in segmental demyelination and impairment of nerve conduction. This gradual process of segmental demyelination has been confirmed histologically in the bladder and is consistent with the observed impairment of nerve conduction of the visceral afferent fibres within the bladder wall. Van Poppel et al. [32] reported that there was less acetylcholinesterase activity in bladder biopsy specimens from patients with severe insulin-dependent DM than in normal controls.

The deficiency of axonal transport of NGF may be important in inducing DM neuropathy, which contributes to DM cystopathy [2,13]. Sasaki et al. [33] recently reported, using STZ-DM rats, the relation between bladder function and NGF levels in the bladder and lumbosacral dorsal root ganglia (DRG), which contain afferent neurones innervating the bladder, and the feasibility of NGF gene therapy for treating DM cystopathy [34] (Fig. 3).

Using STZ-DM rats (65 mg/kg, intraperitoneal) the effects of DM and gene therapy, using replication-defective herpes simplex virus (HSV) vectors encoding the NGF gene (HSV-NGF) injected into the bladder wall, were assessed on Aδ afferent fibre-dependent conscious voiding and C-fibre-mediated bladder nociceptive responses. This was done using metabolic cage/awake cystometry and cystometry with intravesical instillation of 0.25% acetic acid under urethane anaesthesia, respectively. In addition, NGF levels in the bladder and L6–S1 DRG were measured by ELISA methods 3, 6, 9 and 12 weeks after STZ injection, and 4 weeks after the HSV-NGF treatment [33].

In DM rats, NGF levels in the bladder and L6–S1 DRG significantly decreased 12 weeks after STZ injection. In cystometry and metabolic-cage studies, bladder capacity and postvoid residual volume were significantly increased 12 weeks after STZ injection (Fig. 3). Bladder nociceptive responses, assessed by a reduction of intercontraction intervals after acetic acid instillation, were significantly decreased in a time-dependent manner during the 12 weeks after STZ injection.

Rat injected with HSV-NGF into the bladder wall 8 weeks after STZ injection had a significant increase in NGF levels in the bladder and L6 DRG 4 weeks after HSV-NGF treatment (i.e. 12 weeks after STZ injection). DM rats injected with HSV-NGF also had a significantly smaller bladder capacity and postvoid residual volume than DM rats injected with HSV encoding the LacZ gene [Fig. 3]. However, HSV-NGF treated rats showed no significant bladder nociceptive responses after intravesical acetic acid infusion [34,35].

These results indicate that the reduced production of NGF in the bladder and/or impaired transport of NGF to L6–S1 DRG may be an important mechanism inducing DM cystopathy, which is attributable to defects in both Aδ-fibre and C-fibre bladder afferent pathways. NGF gene therapy using replication-defective HSV vectors, which
returns decreased NGF expression in the bladder afferent pathways, could be effective for treating DM cystopathy. [13,35] (Fig. 4).

UROTHELIAL DYSFUNCTION IN DM

The location of the urothelium suggests that it is important for regulating permeability, transport and endocytosis. However, it has become increasingly clear that the urothelium is not only a passive barrier against urea and ion diffusion, but that it can also function as a sensor, controlling bladder function and dysfunction. The urothelium may have receptors and ion channels similar to those in bladder nerves, and injury or inflammation may alter the response of both urothelial cells and sensory afferents to noiceptive and other stimuli. Many mediators, e.g. ATP, NO and prostanoids, can be released from the urothelial cells. Vanilloid receptors are expressed on urothelial cells, and it has been shown that ATP can potentiate the response to vanilloids by lowering the threshold for, e.g. protons and capsaicin. This means that the large amounts of ATP released from damaged/sensitized cells in response to injury/inflammation may influence afferent nerves and contribute to the variety of abnormalities in DM-induced bladder dysfunction.

In the STZ-DM rat model there are progressive increases in total bladder tissue with hypertrophy of the bladder wall and dilatation of the bladder. Both smooth muscle and urothelium (percentage of total tissue) increase significantly in a time-dependent manner. Pinna et al. [15] found that the epithelium from STZ-DM rat bladders was at least twice as thick and heavy as that from controls. In isolated urothelial layer preparations from bladders of STZ-DM rats, the absolute amount of endogenous prostaglandins E₂ and F₂α was higher than in corresponding preparations from control animals, but when prostaglandin F₂α production was expressed as a fraction of tissue weight, it was reduced in the diabetic epithelium.

ATP and bradykinin significantly increased the endogenous release of both prostaglandins from the urothelium when compared with the release under basal conditions. This increase was time-dependent and was higher in diabetic than in control tissues. Bradykinin-induced release of prostaglandin E₂ has also been reported in primary cultures of human urothelial cells. Pinna et al. [15] showed that ATP evoked a phasic and tonic contraction in bladder strips from non-diabetic rats; in preparations from DM, but not from normal animals, the tonic contraction was abolished by removing the urothelium. Bradykinin evoked a long-lasting tonic contraction that was reduced significantly by removing the urothelium only in DM rat bladders. Part of the effects of both ATP and bradykinin on DM bladders thus seemed to depend on the generation and release of prostaglandins from the urothelium. This implies that both ATP (P₂X) and bradykinin receptors might be present in the urothelium, and that these receptors may be important in, e.g. prostaglandin generation and release. In turn, prostaglandins may sensitize sensory nerves and increase the sensitivity of bladder smooth muscle to contractile stimuli, which may contribute to some of the bladder abnormalities, e.g. detrusor overactivity, observed in DM.

The urothelium may also be important in DM-related UTI. It was reported that women with DM have bacteriuria more often than women without. Geerlings et al. [41] showed that Type 1 fimbriated Escherichia coli adhered twice as well to diabetic as to control epithelial cells. The receptors for these Type 1 fimbriae are glycoproteins (uroplakins), and it was proposed that diabetic urethelial cells have a different glycosylation of the receptor on their cells, resulting in higher adherence.

CONCLUSIONS

Although urological complications and major health problems in men and women with DM are common, data to define the expected prevalence, incidence and risk factors, and interventions to reduce the risk of developing these complications, are limited. New research initiatives are needed to further understand the basic disease mechanisms, to develop safe and effective interventions, and to treat the urological complications of DM. A better understanding of the biology of how DM affects the muscle, nerve and urothelium of the urinary bladder could lead to improved treatment options.
FIG. 4. The relationship between bladder function and NGF. (i) In conditions of peripheral neuropathy such as DM, reduced NGF production in the bladder or deficiency in NGF transport to the bladder afferent pathway is an important factor in the pathogenesis of diabetic cystopathy that induces bladder hyporeflexia and decreased sensation. NGF supplement therapy may be useful to restore bladder function in these conditions. (ii) In conditions of bladder hypertrophy induced by BOO, spinal cord injury or bladder inflammation, there is increased NGF that can induce detrusor overactivity and bladder pain. Reducing NGF expression may be effective in normalizing bladder function in these conditions.

REFERENCES

21 Kubota Y, Nakahara T, Mitani A, Maruko T, Sakamoto K, Ishii K.

22 Longhurst PA, Kauer J, Levin RM. The ability of insulin treatment to reverse or prevent the changes in urinary bladder function caused by streptozotocin-induced diabetes mellitus. General Pharmacol 1991; 22: 305–11


27 Longhurst PA, Levendusky MC, Bezuijen MW. Diabetes mellitus increases the rate of development of decompensation in rats with outlet obstruction. J Urol 2004; 171: 933–7


40 Zenser TV, Thomasson DL, Davis BB. Characteristics of bradykinin and TPA increases in the PGE2 levels of human urothelial cells. Carcinogenesis 1988; 9: 1173–7


Correspondence: Michael B. Chancellor, 3471 Fifth Avenue, Suite 700, Pittsburgh, PA 15213, USA.
e-mail: chancellormb@msx.upmc.edu

Abbreviations: DM, diabetes mellitus; STZ, streptozotocin; NGF, nerve growth factor; EFS, electrical field stimulation; NOS, nitric oxide synthase; DRG, dorsal root ganglia; HSV, herpes simplex virus.
Molecular prognostic factors in bladder cancer

MAURIZIO BUSCARINI, MARCUS L. QUEK, PARKASH GILL*, GUANGBIN XIA*, DAVID I. QUINN* and JOHN P. STEIN

Departments of Urology and *Medical Oncology, Kenneth Norris Jr. Comprehensive Cancer Center, University of Southern California Keck School of Medicine, Los Angeles, California, USA

Accepted for publication 11 October 2004

KEYWORDS
bladder neoplasms, tumour markers, transitional cell

INTRODUCTION
Cancer cells are distinguished from normal cells by several hallmarks, including evasion of apoptosis, self-sufficiency in growth signalling, insensitivity to antitumour signals, sustained angiogenesis, limitless replicative potential, propensity towards tissue invasion and metastasis [1]. The molecular and genetic changes in TCC of the bladder can be broadly classified into three interrelated processes: (i) chromosomal alterations, triggering the initial carcinogenic event; (ii) tumour proliferation, caused by loss of cell-cycle regulation and derangements in normal apoptotic turnover; and (iii) metastasis, in which the initial tumour spreads to distant sites, bringing into play processes such as angiogenesis and loss of cellular adhesion.

The accumulation of these successive genetic alterations, rather than a single genetic event, determines a tumour’s phenotype and ultimately the patient’s clinical outcome [2]. Herein we summarize recent publications on some of the more promising molecular markers for prognostication in bladder cancer and comment on potential clinical applications.

THE CARCINOGENESIS OF BLADDER CANCER
ONCOGENES
Oncogenes are normal cellular genes that can become altered by various genetic insults, resulting in a malignant phenotype, either by overexpression of the normal gene product or by expressing a protein product with altered function [1]. Oncogenes thought to be important in human bladder cancer include cH-ras and HER2/neu. Mutations in the H-ras gene have been implicated in the development and progression of human bladder cancer. Alterations involving codons 12 and 61 of the ras oncogene have been found in up to 39% of bladder cancers [3]. A potential prognostic role for the cH-ras oncogene was suggested by Fontana et al. [4], where overexpression of the cH-ras oncogene was correlated with early recurrence in patients with superficial bladder cancer. Complete loss of p53 is a prerequisite for collaborating with cH-ras to promote bladder cancer [5].

The HER2/neu oncogene encodes a transmembrane glycoprotein similar to epidermal growth factor (EGF) receptor, having tyrosine kinase activity [6] and the ability to stimulate cellular growth. Several studies noted an association between HER2/neu expression and higher stage tumours [7], tumour progression, greater incidence of metastatic disease and reduced overall survival.

TUMOUR-SUPPRESSOR GENES
Deletions of chromosome 9 are the most common chromosomal abnormalities associated with bladder cancer. Given that deletions of chromosome 9 are found with both superficial and muscle-invasive disease, this alteration may represent an early event in the molecular pathogenesis of TCC [8]. Other notable chromosomal deletions have been detected on chromosomes 13 (at the retinoblastoma, Rb, gene) and 17 (at the p53 gene).

Most chromosome 9 deletions involve the 9p21 locus (INK4a/ARF and INK4b) which encodes for three distinct proteins, i.e. p16INK4a, p14ARF and p15INK4b. Each of these proteins acts as a negative cell-cycle regulator, and they are therefore considered potential tumour-suppressor genes. Chromosome 9 losses occur early in bladder oncogenesis and before p53 alterations or development of aneuxomy [9,10].

On chromosome 13, Rb gene mutations are found in 25–30% of bladder tumours and loss of heterozygosity at the Rb locus (13q14) is associated with an absence of Rb protein expression by immunohistochemical techniques.

On chromosome 17, a well-recognized chromosomal alteration involves the tumour-suppressor gene at 17p13 (p16). Olumi et al. [11] reported the high frequency of loss of heterozygosity at chromosome 17p in high-grade TCC. Genetic defects in the p53 locus have been shown to correspond with protein expression of the mutated p53 gene product.

CELL-CYCLE REGULATORY PATHWAYS
Tumour proliferation depends on the derangement of normal cell-cycle progression and control. Cell cycle-associated protein complexes composed of cyclins and cyclin-dependent kinases regulate normal cellular proliferation [11]. As previously mentioned, several tumour-suppressor genes and their protein products (p53, pRb, p27Kip1, p16INK4a and p14ARF) act at the G0/G1 checkpoint of the cell cycle to prevent loss of cell-cycle control, and ultimately lead to tumour progression.

Gene alteration may occur by mutation, deletion or methylation, but in most cases, phenotypic expression requires the alteration of both gene copies. One gene copy may be inherently altered, followed by an environmental mutagen; or both copies may be affected by two independent somatic events, leading to expression of the altered gene product. One notable exception to this ‘two-hit’ model of carcinogenesis is the tumour-suppressor gene p53, in which alteration of only one copy is sufficient to alter function.

TUMOUR-SUPPRESSOR GENES
The interaction of several tumour-suppressor genes leads to alterations in cell-cycle regulatory pathways. The Rb gene, at 13q14, encodes for a nuclear phosphoprotein that normally acts at the G1/S checkpoint to
inhibit cell cycle progression. The interaction of the Rb-encoded protein with various cell-cycle regulatory proteins allows for normal cellular proliferation, while alterations with these protein interactions can subsequently lead to uncontrolled cell growth. Functional reduction of Rb is associated with progression of bladder cancer to a more malignant and aggressive behaviour [12]. Further evidence for this was reported from studies by Cordon-Cardo et al. [13], in which loss of Rb immunoreexpression was associated with significantly shorter survival in patients with muscle-invasive bladder tumours.

The p53 gene, at 17p13, encodes for a protein vital to arresting the cell cycle [14]. When DNA damage is detected, the level of p53 protein increases, leading to cell-cycle arrest. This necessarily allows for DNA repair and prevents propagation of DNA defects. Mutations in p53 result in the production of a dysfunctional protein product with a longer half-life than the wild-type protein. Because of this difference in protein longevity, p53-mutated gene products accumulate in the cell nucleus and can be easily detected by immunohistochemical methods.

Esrig et al. [15] evaluated p53 nuclear immunoexpression in 243 patients with invasive bladder cancer treated uniformly with radical cystectomy. Altered p53 expression was associated with a significantly greater risk of disease recurrence and reduced overall survival than in patients with wild-type p53 expression, and nuclear accumulation of p53 was found to be an independent predictor of disease progression. A prospective randomized multi-institutional trial is currently underway to determine the impact of chemotherapy in organ-confined bladder cancer based on p53 status.

Given the apparent prognostic value of absent Rb expression and p53 nuclear accumulation in bladder cancer, two independent studies sought to determine whether combining these two markers could better stratify patients with bladder cancer. Indeed, tumours with alterations in both p53 and Rb are associated with a poorer prognosis than tumours with normal wild-type p53 and Rb genes. Tumours with alterations in only one of these genes behaved in an intermediate fashion. These studies suggest an independent, yet synergistic role for both p53 and Rb expression in the progression of bladder cancer.

Not all p53 mutated bladder tumours recur or progress. Indeed, p53 mediates its effects on the cell cycle through regulating p21 expression [15]. Therefore, alterations in p53 may lead to loss of p21 expression and subsequently unregulated cell growth.

Stein et al. [16] evaluated 101 patients with p53-altered tumours treated with radical cystectomy, and found that loss of p21 expression was associated with higher recurrence rates and lower overall survival than p21-positive tumours. While several other groups have subsequently questioned the prognostic value of p21 expression through p53-independent pathways may influence cell-cycle control, and that tumours with both p53 alterations and loss of p21 expression appear to have a poorer prognosis. These patients may be candidates for more aggressive adjuvant therapeutic regimens.

Reduced expression of p27 and cyclins D and E correlates with increased grade, stage and mortality in bladder cancer [17]. Several groups have reported data suggesting that low p27 expression with or without low cyclin E expression is adversely prognostic in bladder cancer [18]. Decreased p27 expression is prognostic in several cancers, including breast, prostate and nonsmall cell lung cancer, and is usually associated with increased cyclin E expression. Juan and Cordon-Cardo [19] recently described disruption of the nucleoplasm-nucleolar shuttling of cyclin E in bladder cancer cell lines, suggesting that altered intranuclear localization of cyclin E rather than overexpression may be a distinguishing feature of progressive bladder cancer. Overexpression of a low molecular weight cyclin E was recently reported to be a major prognostic factor in breast cancer. Interestingly, loss of p27 expression in superficial bladder cancer correlates with disease recurrence and invasion, as does low expression of cyclin D1. Patients with low cyclin D1, low p27 and a high proliferative index measured by Ki67 expression had an extremely high rate of recurrence.

ANGIOGENESIS AND LOSS OF CELL ADHESION

Angiogenesis is the process by which new blood vessels are formed from the surrounding established vasculature. During normal development and physiological repair, this event proceeds in a tightly regulated manner [20]. Neoplastic conditions also require angiogenesis (neovascularization) to maintain their malignant growth and metastatic potential. Therefore, inhibiting tumour angiogenesis may provide another avenue for therapeutic benefit.

Under most homeostatic conditions angiogenesis is an infrequent process, controlled by an abundant array of inhibitory signals directed at the endothelium, thereby tipping the balance towards neovascular quiescence. Therefore, within a tumour's microenvironment, the balance between various stimulatory and inhibitory inputs to the endothelial cells determines its ability to induce angiogenesis, thus providing the necessary nutrients for continued growth and eventual metastasis.

Several mechanisms are thought to be involved in tumour angiogenesis, including overexpression of various inducers and loss of endogenous inhibitors [21]. These factors may be produced by the tumour cells themselves or released from the surrounding extracellular matrix and tumour-associated stromal cells, or they may be products of the host inflammatory cells that infiltrate the tumour.

MICROVESSEL DENSITY

Given the role of angiogenesis in tumour growth and spread, one concept that may provide prognostic information is the 'microvessel density' within and around a given tumour. By measuring antibodies to factor VIII and CD34 that recognize immature or new vascular endothelial cells, it is possible to quantify the degree of angiogenesis taking place. Microvessel density counts have been correlated with bladder cancer progression and overall survival [22].

ANGIOGENIC INDUCERS

Several human cancers have high levels of growth factors and their receptors that can be used as potential therapeutic targets. Urothelial tumours overexpress tyrosine kinase receptors such as the receptors for EGF (ErbB-1), vascular endothelial growth factor (VEGF) and Her2/neu (ErbB-2). Systemic administration of inhibitors blocks the growth of bladder cancer and enhances the activity of conventional chemotherapy. Several trials are now ongoing, testing agents such as
herceptin (anti-HER2), IMC225 cetuximab, ZD 1389 Iressa and OSI-774 Tacevra (EGF receptor inhibitors).

VEGF is present in higher concentrations in the urine of patients with bladder cancer than in controls, and VEGF levels are correlated with tumour recurrence in patients with Ta and T1 disease [23]. Williams et al. [24] also reported higher levels of VEGF in the urine of patients with high-grade and/or muscle-invasive TCC than in those with prostate cancer or no malignancy. In those patients undergoing radical cystectomy, higher preoperative urinary VEGF was associated with a lower 3-year survival. In a series of patients with locally advanced bladder cancer and undergoing cystectomy, expression of VEGF and E-cadherin was strongly related to disease-specific survival.

Increased cyclooxygenase-2 (COX-2) expression has been the focus of considerable interest as a prognostic marker, because of the potential to specifically target this pro-angiogenic molecule with inhibitors [25,26]. Recent experimental work suggests that COX-2 may reduce the cytotoxic effects of chemotherapy. High expression of COX-2 is associated with shorter survival in patients receiving chemotherapy after cystectomy. Trials of COX-2 inhibitors as preventative and therapeutic agents in bladder and other cancers are ongoing [27].

ANGIOGENIC INHIBITORS

Although several endogenous inhibitors of angiogenesis exist, thrombospondin-1 (TSP-1) has been examined most in human bladder cancer. It was shown that normal urothelial cells contain high levels of TSP-1, and that cancer cells have been shown to induce the production of the angiogenesis-inducer scatter factor by the underlying stromal cells. Matrix metalloproteinases (MMPs) are also intimately involved in tumour-associated degradation of the extracellular matrix. Two of these factors, MMP-2 and MMP-9, are elevated in the serum and urine of patients with muscle-invasive TCC, and correlate with decreased disease-free survival. MMP-9 expression was also higher in TCC than in normal urothelium, and directly related to increasing tumour stage [29].

CD44 is a widely expressed cell-surface adhesion molecule involved in cell-cell and cell-matrix interactions, as well as signal transduction through ras in response to hyaluronic acid. Expression of CD44 is increased in superficial TCC, with a decrease in expression at the time of muscle invasion. Recent data suggest that CD44 status is prognostic in urothelial cancer [30].

EXTRACELLULAR MATRIX AND METASTASIS

The extracellular matrix provides the scaffolding for endothelial attachment and subsequent capillary formation. Bladder cancer cells have been shown to induce the production of the angiogenesis-inducer scatter factor by the underlying stromal cells. Matrix metalloproteinases (MMPs) are also intimately involved in tumour-associated degradation of the extracellular matrix. Two of these factors, MMP-2 and MMP-9, are elevated in the serum and urine of patients with muscle-invasive TCC, and correlate with decreased disease-free survival. MMP-9 expression was also higher in TCC than in normal urothelium, and directly related to increasing tumour stage [29].

CD44 is a widely expressed cell-surface adhesion molecule involved in cell-cell and cell-matrix interactions, as well as signal transduction through ras in response to hyaluronic acid. Expression of CD44 is increased in superficial TCC, with a decrease in expression at the time of muscle invasion. Recent data suggest that CD44 status is prognostic in urothelial cancer [30].

CONCLUSIONS

The translational application of molecular markers for bladder cancer prognostication continues to develop. A tumour’s ability to grow, invade and spread depends on a multitude of complex interactions that are only now being slowly elucidated at the molecular level. It is unlikely that a single molecular marker will provide adequate insight into a tumour’s biological potential. The ultimate application of tumour markers may involve the evaluation of numerous molecular endpoints in a ‘test battery’ approach. This strategy may provide a more accurate assessment of a tumour’s phenotype, including responsiveness to both surgical and medical therapeutics.

Currently, the conventional histopathological assessment of grade and stage allows for only a gross stratification of clinical outcomes for patients with bladder cancer. Despite significant research in the molecular understanding of neoplasia, the promise of accurate predictions of tumour behaviour based on molecular markers is yet to be realized. The recent development of techniques to interrogate tumours for the expression of a myriad genes in multiple tissue sites simultaneously, with linkage to outcome data and other clinical variables, promises to deliver a new level of prognostication and prediction for several cancers. Molecular techniques will continue to develop and clinical trials testing the strongest candidate markers will be necessary to bring this understanding of the basic science of tumour biology to clinical decision-making and patient care.

CONFLICT OF INTEREST

None declared. Source of funding: American Italian Cancer Foundation.

REFERENCES

1 Hanahan D, Weinberg RA. The hallmarks of cancer. Cell 2000; 100: 57–70


Correspondence: John P. Stein, Department of Urology MS#74, University of Southern California Keck School of Medicine, Kenneth Norris Jr. Comprehensive Cancer Center, 1441 Eastlake Avenue, Suite 7414, Los Angeles, California 90089, USA. e-mail: stein@hsc.usc.edu

Abbreviations: EGF, epidermal growth factor; Rb, retinoblastoma (gene); VEGF, vascular endothelial growth factor; COX-2, cyclooxygenase-2; TSP-1, thrombospondin-1; MMP, matrix metalloproteinase.
An evidence-based approach to understanding the pharmacological class effect in the management of prostatic diseases

CHRISTOPHER P. EVANS, NEIL FLESHNER*, JOHN M. FITZPATRICK† and ALEXANDER R. ZLOTTA‡

University of California, Sacramento, CA, USA; *Princess Margaret Hospital, Toronto, Canada; †Mater Hospital and Conway Institute, University College, Dublin, Ireland and ‡University Clinics of Brussels, Erasme Hospital, Brussels, Belgium

Accepted for publication 5 December 2004

INTRODUCTION

Ever more alternative products are available for each drug type commonly used to treat prostatic diseases, i.e. α-blockers, 5α-reductase inhibitors, antiandrogens and LH-RH agonists. Once a urologist has decided which type of drug to use, their decision about which specific agent to prescribe will depend on several factors, including dosing regimen, delivery mechanism, speed of onset, treatment costs, local prescribing habits, marketing, patient choice, personal experience and published reports. Ideally, evidence-based medicine (EBM) should be the main factor in treatment choice. This review sets out the principles of EBM and examines the best available evidence for drugs that are commonly prescribed to treat BPH or prostate cancer. We consider whether a class effect can be shown for any of these groups of drugs and if class effects should be accepted in clinical practice. We focus on efficacy, but tolerability can also be an important factor when choosing between drugs of the same class, and will be discussed where relevant.

PRINCIPLES OF EBM

EBM has been described as the ‘conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients’ [1]. For the clinician, this means identifying the best available evidence from a vast number of published medical reports, assessing whether it is applicable to the individual patient and then using it in clinical practice [2]. Of the types of published evidence available, systematic reviews or meta-analyses of well-designed randomized controlled trials (RCTs), followed by individual RCTs and well-designed non-randomized studies are considered the most robust, reliable and therefore valuable [3]. Less robust evidence from case reports, clinical examples, or consensus meetings may also be considered.

Systematic reviews integrate otherwise unmanageable amounts of information from primary investigations in a way that limits bias and random error; meta-analyses allow an evaluation of consistency of findings and, if quantitative, may increase the accuracy of estimates of treatment effects [4]. As such, both should be useful tools in clinical decision-making. However, systematic reviews and meta-analyses are not always possible. For trials to be combined in a systematic review or meta-analysis, there needs to be a sufficient number of similar studies, i.e. with analogous study designs in patients with similar disease states and assessing comparable clinically relevant outcomes. Whether trials are combined in a systematic review or meta-analysis, or examined for their individual merit, their design, endpoints and reporting quality need careful examination to determine the most appropriate and robust data. Trials must be of a high quality to avoid bias, sufficiently large enough to give a reliable answer, of good validity, and the population studied should allow the results to be clinically applicable.

One of the most important factors is randomization to exclude selection bias; it has been estimated that not randomizing can lead to an overestimation of treatment effect by 40% [5]. Other factors (and their percentage overestimation) include small trials (30%), poor reporting quality (25%), duplicate reporting (20%), and lack of blinding (17%). Questions have been raised as to whether study sponsorship may also introduce bias and there are concerns that the process of publication itself can lead to bias in favour of positive results.

Although many clinical trials are conducted ‘blind’ to minimize observer bias, this is not always a realistic option. For example, in prostate cancer trials, it would not be reasonable to carry out sham orchidectomy or radiotherapy, and characteristic treatment effects, such as hot flushes with LH-RH agonists, can effectively ‘un-blind’ a study. The more patients in a trial, the more accurately the size of a clinical effect can be assessed and the less likely the result is to be a result of random chance. The amount of information needed to avoid an incorrect conclusion depends on the size of the effect being studied and the level of certainty required. To be valid, a trial must be of an appropriate design to answer the question addressed; validity is based on criteria such as use of clinically important outcomes and duration of intervention and observation.

IS THE CLASS EFFECT EVIDENCE-BASED?

Drugs are generally considered to be in the same class if they have a similar chemical structure and mechanism of action, and if they confer similar pharmacological effects. However, compounds with very similar structures can have different properties. For example, dihydrotestosterone differs from testosterone by only one hydrogen atom, but has a much greater binding affinity for the androgen receptor, resulting in different effects on gene expression. Consequently, the notion of a pharmacological ‘class effect’ should be considered with caution. Indeed, there is no universally accepted definition. A class effect is usually taken to mean that drugs in a class have similar therapeutic
effects and similar safety and tolerability, both in nature and extent [3]. If such a class effect exists, it would be likely that the least costly agent in each class would be the first choice. However, it is clear that no matter how strong the pathophysiological rationale or indirect evidence, the efficacy and safety of a new drug must be established in clinical outcome studies, and the equivalency of untested drugs even in a well-established ‘class’ should be considered unconfirmed.

For some products routinely used in prostate medicine, comparative data are limited, but prescription is still widespread based on the assumption of a class effect. To take an evidence-based approach to establishing a class effect, RCTs of direct comparisons of drugs within the class are needed [3]. However, this level of evidence is rarely available.

The next best level of evidence includes indirect comparisons across two or more placebo-controlled trials. In this case, only proportional effects such as the relative risk reduction can be compared. A class effect is considered to be present when drugs with similar mechanisms of action generate relative risk reductions (or odds ratios) that are similar in direction and magnitude [3]. However, such comparisons are less useful in determining whether one drug is more effective than another, because the comparison is between different cohorts of patients and the advantages of randomization are lost [3]. Decisions about the level of evidence necessary to establish a class effect are, necessarily, individual choices, which take into account local circumstances and personal comfort levels [3].

**BPH**

In BPH, relief from symptoms is the key aim, with medical therapy being the first-line treatment for most men with symptomatic BPH. The two drug classes commonly used are α-blockers and 5α-reductase inhibitors, which aim to reduce LUTS by decreasing smooth muscle tone in the prostate and bladder, or by reducing prostate size, respectively.

**α-BLOCKERS**

The α-blockers are the most frequently used prescription medication for BPH; the class includes tamsulosin, terazosin, alfuzosin, doxazosin and prazosin, which have different selectivity for the α1-adrenoceptor subtypes. Systematic reviews have been published for tamsulosin and terazosin, and a pooled analysis for alfuzosin (Table 1) [6–8]. These reports, in agreement with an earlier meta-analysis by Djavan and Marberger [9], conclude that the α-blockers are effective and consistently improve LUTS and urinary flow compared with placebo.

α-Blockers have been directly compared in a few small trials (involving 50–256 patients) [9–12]. A review of trials directly comparing tamsulosin with terazosin found that these agents are equally effective in improving symptoms [7,8]. No definitive conclusions about differences in efficacy can be made from these studies; all α-blockers, whether selective or not, seem to have similar efficacy in short-term trials [9]. The data suggest that α1-blockers, such as terazosin or doxazosin, give similar improvements as subtype-selective α1A-blockers, like tamsulosin, in peak urinary flow rates and symptom scores after 4 weeks of treatment. From these studies it might be concluded, on the basis of efficacy, that there possibly is a class effect. However, there are differences in tolerability, with tamsulosin better tolerated than doxazosin, prazosin and terazosin, as measured by withdrawals from treatment [9]. These may be related to different pharmacokinetic properties and adrenoceptor subtype selectivity, and contradict the concept of a class effect.

**5α-REDUCTASE INHIBITORS**

For the last decade, finasteride, which acts on the type-2 isoenzyme of 5α-reductase, has been the only available 5α-reductase inhibitor. A recent systematic review of finasteride included 19 placebo-controlled trials of 3–48 months’ duration (14 729 patients) [13]. The studies were of high quality, most were ≥1 year in duration, and most of the larger trials showed benefits in symptom score, maximum urinary flow rate and prostate volume for finasteride over placebo (P < 0.01; Table 1) [13,14].

Dutasteride, which inhibits both isoenzymes of 5α-reductase, was launched in the USA in 2003. The results of three large, double-blind RCTs of dutasteride including 4325 men were recently reported (Table 1) [14]. Dutasteride and finasteride have not been formally compared and no definitive conclusions can currently be drawn about any differences between them. While dutasteride is said to inhibit serum 5α-reductase to a greater extent than finasteride, the significance of this may be limited, as it is prostatic stromal intracellular 5α-reductase that mediates gene transcription for growth factor genes. Therefore, although the data support the efficacy of both finasteride and dutasteride in BPH, there is as yet insufficient evidence to address the question of whether a class effect exists for the 5α-reductase inhibitors.

α-BLOCKERS COMBINED WITH 5α-REDUCTASE INHIBITORS

The long-term efficacy of the α-blocker doxazosin and the 5α-reductase inhibitor finasteride, as monotherapy or combined, was evaluated in a randomized, long-term, double-blind placebo-controlled trial [15]. While each agent reduced the risk of overall clinical progression, combined therapy was significantly more effective than either monotherapy. This trial was of excellent design, yet raises several interesting issues about the class effect. For example, is it appropriate to extrapolate the role of doxazosin to other α-blockers? The trial was designed for an intent-to-treat analysis, which in theory mimics ‘real-world clinical medicine’, but 27% of patients in the doxazosin arm could not tolerate even 4 mg and were withdrawn from therapy. In clinical practice these patients would probably have been switched to an α1A-subtype-selective drug such as tamsulosin. Examining the number of side-effects that occurred statistically significantly more often than with placebo, there were five with doxazosin, three with finasteride and nine with combined therapy. However, only 18% of patients in the combined arm discontinued treatment. Potential explanations for this include the possibility that the better efficacy resulted in patients tolerating an increase in side-effects, or it may have been the case that patients had to discontinue both drugs to be counted as off treatment. Thus, the intent-to-treat concept, drug tolerability and definition of discontinuation are potentially contributing to the outcomes reported. Assuming a class effect, a clinician may deduce that tamsulosin, with lower discontinuation rates than doxazosin, would be better for combined therapy. This reasoning, while deductive, is not actually evidence-based.
PHARMACOLOGICAL CLASS EFFECT IN MANAGING PROSTATIC DISEASES

TABLE 1 Systematic reviews and pooled analyses of α-blockers and 5α-reductase inhibitors in the treatment of patients with LUTS suggestive of BPH

<table>
<thead>
<tr>
<th>Ref</th>
<th>Treatment(s)</th>
<th>Study [N men]</th>
<th>Duration of study</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>[6]</td>
<td>Alfuzosin vs placebo</td>
<td>PA including 11 RCTs (1470)</td>
<td>1–6 months</td>
<td>Significant reduction in PVR: at 6 months, 36.8 mL (28%) for alfuzosin vs 22.6 mL (16%) for placebo (P &lt; 0.001)</td>
</tr>
<tr>
<td>[7,8]</td>
<td>Tamsulosin vs terazosin</td>
<td>SR including 4 trials (402)</td>
<td>4–9 weeks</td>
<td>Mean IPSS improvement from baseline 4% for terazosin vs 40% for terazosin. Peak urine flow increased by 29% for tamsulosin vs 25% for terazosin</td>
</tr>
<tr>
<td>[9]</td>
<td>Alfuzosin, terazosin, doxazosin, tamsulosin</td>
<td>Meta-analysis of data from 21 placebo-controlled studies and 4 comparative studies</td>
<td>1–12 months</td>
<td>Total USS improved 30–40% and maximum urinary flow rate by 16–25% with α-blocker treatment. No efficacy comparisons between the different agents</td>
</tr>
<tr>
<td>[10]</td>
<td>Dutasteride vs placebo</td>
<td>SR including 4 trials (694)</td>
<td>4–12 months</td>
<td>Mean change 1.2–4 mL/s for tamsulosin vs 1.1 mL/s for placebo. Significant improvement in peak urine flow in 8/9 studies: mean improvement 2.2 mL/s for terazosin and 1.1 mL/s for placebo</td>
</tr>
<tr>
<td>[11]</td>
<td>Finasteride vs placebo</td>
<td>SR including 19 RCTs (14 729)</td>
<td>3–48 months</td>
<td>Most large trials* showed that finasteride was better than placebo for USS (3.7 points less for finasteride vs 2.3 for placebo at 1 year), maximum urinary flow rate (+1.3 mL/s finasteride vs 0.8 mL/s placebo at 2 years) and prostate volume (25% less for finasteride vs 4% less for placebo at 2 years)</td>
</tr>
<tr>
<td>[12]</td>
<td>Dutasteride vs placebo</td>
<td>Combined results of three double-blind RCTs of identical design (4325)</td>
<td>24 months</td>
<td>Statistically significantly better vs placebo at 2 years in: USS (+2.3 points less for dutasteride vs 2.3 for placebo, P &lt; 0.001); maximum urinary flow (+2.2 mL/s dutasteride vs 0.6 mL/s placebo, P &lt; 0.001); and prostate volume (26% less dutasteride vs 2% more placebo, P &lt; 0.001)</td>
</tr>
</tbody>
</table>

SR, systematic review; USS, urinary symptom score; PA, pooled analysis; PVR, postvoid residual; IPSS, International Prostate Symptom Score; *Except a study that included men with small prostates.

PROSTATE CANCER

Survival is recognized as a key endpoint in trials of anticancer agents, and in contrast to endpoints in trials in other fields, differences in outcome of just 2–3% may be of considerable clinical importance. However, detecting statistically significant differences at this level requires clinical trials involving many patients and, commonly, studies are not powered well enough to detect such small differences. In the case of a highly prevalent disease such as prostate cancer, differences in the 2–3% range can result in a large gain in life across the population. If such differences are observed between agents within the same class this could be sufficient to suggest that a class effect should not be assumed, but that agents should be assessed on individual merits.

LHRH AGONISTS

There have been few direct comparisons of LHRH agonists, and from which no definitive conclusions can be made. One randomized study of reasonable size (>40 patients per arm) was conducted, comparing the efficacy, safety and testosterone pharmacodynamics of 1-month formulations of triptorelin (3.75 mg) and leuprolelin (7.5 mg) [16]. Men with advanced prostate cancer (stage C or D) in the intent-to-treat population received either triptorelin (137 men) or leuprolelin (140 men) for 9 months. Triptorelin induced castrate levels of testosterone at a slower rate than leuprolelin, but maintained castration as effectively [16]. There was no evidence that the slower onset of castration with triptorelin was deleterious, indeed the 9-month survival rate showed a small difference favouring triptorelin (97.0% vs 90.5%, P = 0.033), but a longer follow-up is required. This study highlights that similar levels of testosterone suppression do not necessarily indicate similar levels of clinical efficacy, and that use of castrate levels of testosterone as a surrogate marker for survival may not be appropriate. A further point is that the monthly dose of leuprolelin licensed for use in most countries is 3.75 mg, in contrast to the dose of 7.5 mg used in that study; therefore, conclusions made on the basis of that study may not reflect true clinical practice in many parts of the world.

As there are few direct comparative data, indirect evidence from RCTs comparing the various LHRH agonists with other...
RCTs with ≥40 patients per arm that compared LHRH agonists with DES or CPA are also shown in Table 2 [22–27]. In comparisons with DES, none of the studies showed a significant survival difference between treatments. Studies of LHRH agonists vs CPA have only been conducted with goserelin and, while no survival data were reported, Thorpe et al. [26] reported a benefit in time to progression favouring goserelin over CPA (P = 0.016; Table 2).

In a meta-analysis that included 12 trials comparing LHRH agonist monotherapy with orchidectomy or DES, the overall hazard ratio (HR) for survival with LHRH agonists relative to orchidectomy suggested that LHRH agonists are essentially equivalent to orchidectomy in terms of survival [4]. Although none of these trials directly compared the three LHRH agonists, indirect comparison of seven goserelin studies [1137 men], four buserelin studies [308 men], and one leuprorelin study [94 men] found that HRs for survival with the individual agents relative to orchidectomy were similar.

### Adjuvant therapy

There have been no systematic reviews of LHRH agonists as adjuvant therapy. A recent analysis of published studies suggested that differences in drug regimen, duration and timing of treatment in trials of adjuvant or neoadjuvant LHRH agonist therapy mean that pooling these trials for meta-analysis would not be possible [28]. However, in individual studies one LHRH agonist, goserelin, has shown a consistent benefit in terms of delaying progression and improving survival, as summarized below.

Goserelin is the only LHRH agonist studied as monotherapy in large (≥40 patients per arm) RCTs of adjuvant hormonal therapy after radiotherapy or radical prostatectomy [Table 3] [29–35]. Adjuvant hormonal therapy with goserelin significantly improved survival in the radiotherapy setting and in node-positive men after radical prostatectomy, and this is good evidence on which to base treatment decisions. However, the optimum timing and duration of therapy remain to be clarified.

#### Neoadjuvant therapy

The rationale for neoadjuvant hormonal therapy is to directly improve outcomes or enhance the primary therapy, e.g. by reducing the dose of radiation or field size, thereby minimizing the adverse effects of radiation. The only randomized study of an LHRH agonist neoadjuvant to radiotherapy is with goserelin, which, combined with flutamide, was associated with a significant improvement in overall survival compared with radiotherapy alone [36] (Table 3). Comparison of hormonal therapy (goserelin plus flutamide) neoadjuvant or adjuvant to radiotherapy, found no significant difference in progression-free or overall survival [37] (Table 3). Although neoadjuvant hormonal

---

**Table 2: RCTs comparing LHRH agonists vs orchidectomy or DES or CPA in the treatment of prostate cancer**

<table>
<thead>
<tr>
<th>Ref</th>
<th>LHRH agonist</th>
<th>N men randomized, vs orchidectomy or DES</th>
<th>LHRH agonist dosing interval</th>
<th>Follow-up, years</th>
<th>Survival, % (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>vs orchidectomy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[17]</td>
<td>Goserelin</td>
<td>148 vs 144</td>
<td>Monthly</td>
<td>2 (median)</td>
<td>42 vs 36 (NS, 0.23)</td>
</tr>
<tr>
<td>[18]</td>
<td></td>
<td>138 vs 145</td>
<td>Monthly</td>
<td>4 (minimum)</td>
<td>29 vs 33 (NS, 0.42)</td>
</tr>
<tr>
<td>[19]</td>
<td>Buserelin</td>
<td>113 vs 118 plus CPA 111</td>
<td>Daily</td>
<td>5.7 (median)</td>
<td>13 vs 10 vs 14 (NS, not available)</td>
</tr>
<tr>
<td>[20]</td>
<td></td>
<td>72 vs 46 vs oestrogens 22</td>
<td>Daily</td>
<td>1</td>
<td>(NS, 0.40)</td>
</tr>
<tr>
<td>[21]</td>
<td>Triptorelin</td>
<td>55 vs 49</td>
<td>Monthly</td>
<td>2</td>
<td>Mean 16 vs 13 months (P not given)</td>
</tr>
<tr>
<td></td>
<td>Leuprorelin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| vs DES |
| [27] | Goserelin     | 124 vs DES 126                           | Monthly                       | >3             | 32 vs 36 (0.88) |
| [22] | Buserelin     | 111 vs DES/orch 56 or MTX + DES/orch (98)| Daily                         | >2             | No difference among groups by log-rank analysis |
| [23] | Leuprorelin   | 105 vs DES 41/orch 14                    | Daily                         | >2             | No difference among groups by log-rank analysis |
| [25] | Triptorelin   | 92 vs DES 94                             | Daily                         | 1              | 87 vs 78 (0.17) |

| vs CPA |
| [26] | Goserelin     | 175 vs CPA 175                           | Monthly                       | 4 (maximum)    | Not reported. Median TTP (days) 346 vs 225 (0.016) |
| [24] | Buserelin     | 152 vs CPA 71                            | Monthly                       | 2              | Median 132 vs 130 weeks (NS) |

|       | Leuprorelin   |                                          |                               |                |               |

*The dose was 1.0 mg daily, compared with the currently licensed doses of 3.75 mg or 7.5 mg per month. NS, not significant; MTX, methotrexate; orch, orchidectomy; TTP, time to progression.*
therapy with radical prostatectomy significantly decreases the positive margin rate, randomized studies have shown no improvement in overall survival [38].

Summary: LHRH agonists

The prevailing data suggest equivalent survival between LHRH agonists and orchidectomy. It is apparent that within the LHRH agonist class, the vast majority of available data are for goserelin, which is associated with benefits in several settings. The amount and quality of evidence that compares goserelin with other members of the class, or that compares LHRH agonists with other treatments, is insufficient to establish a class effect.

### Antiandrogens

Steroidal and nonsteroidal antiandrogens are not members of the same class. These two groups of agents differ in structure and mechanism of action. Steroidal antiandrogens, e.g. CPA, chloramadinone acetate and megestrol acetate, have mixed agonistic and antagonistic activities, while nonsteroidal antiandrogens, e.g. bicalutamide, flutamide and nilutamide, have a pure antiandrogenic effect.

**Monotherapy**

There have been no direct RCTs comparing steroidal antiandrogens, and there are minimal clinical data with chloramadinone acetate and megestrol acetate from which to draw conclusions about any class effect. Similarly, to date, no comparative monotherapy trials of nonsteroidal antiandrogens have been conducted. In the absence of direct comparative data, there are too few RCTs relating to antiandrogen monotherapy to draw any conclusions about a class effect in this setting.

**Combined therapy**

Despite numerous trials investigating combined therapy (medical or surgical castration plus an antiandrogen, otherwise known as maximal androgen blockade), only one randomized, double-blind trial compared combined therapies directly [39]. Of 813 patients, 404 were assigned to bicalutamide combined with an LHRH agonist, and 409 to

---

**TABLE 3 RCTs of adjuvant and neoadjuvant treatment with LHRH agonists in the treatment of prostate cancer**

<table>
<thead>
<tr>
<th>Ref</th>
<th>LHRH agonist, study</th>
<th>Treatment (N patients randomized)</th>
<th>Median follow-up, years</th>
<th>Survival, % (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adjuvant</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[29,31]</td>
<td>Goserelin, EORTC 22863</td>
<td>RT + goserelin 3 years (207) vs RT alone + goserelin after relapse (208)</td>
<td>5.5</td>
<td>5-year, 78 vs 62 (&lt;0.001)</td>
</tr>
<tr>
<td>[32]</td>
<td>Goserelin, RTOG 85–31</td>
<td>RT plus goserelin (488) vs RT alone + goserelin after relapse (489)</td>
<td>7.3</td>
<td>10-year, 53 vs 38 (&lt;0.0043)</td>
</tr>
<tr>
<td>[33]</td>
<td>Goserelin, RTOG 92–02</td>
<td>Flutamide + goserelin for 2 months before and for 2 months during RT then randomized to 2 years of goserelin (753) or no further treatment (761)</td>
<td>5.8</td>
<td>5-year, 80 vs 79 (NS, 0.73) For patients with Gleason score of 8–10 (337), 5-year survival was 81 vs 71 (0.044)</td>
</tr>
<tr>
<td>[34,35]</td>
<td>Goserelin, ECOG 7887/ EST3886</td>
<td>RP + immediate goserelin or orchidectomy (47) or RP alone (51)*</td>
<td>10</td>
<td>10-year, 72 vs 49 (0.025)</td>
</tr>
<tr>
<td>[30]</td>
<td>Goserelin, RTOG 86–10</td>
<td>RT + flutamide and either goserelin (10) or leuprololin (88) for 6 months vs RT alone (104)</td>
<td>4.5</td>
<td>5-year, 88 vs 78 (0.04)</td>
</tr>
<tr>
<td><strong>Neoadjuvant</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[36]</td>
<td>Goserelin, RTOG 94–13</td>
<td>Goserelin + flutamide 2 months before and during RT (226) vs RT alone (230)</td>
<td>6.7</td>
<td>At 8 years, statistically significant improvement in local control (42 vs 30) (0.016), reduction in the incidence of distant metastases (34 vs 46) (0.04), PFS (33 vs 21) (0.004), PSA PFS (24 vs 10) (&lt;0.001) and prostate cancer mortality (23 vs 31) (0.05)</td>
</tr>
<tr>
<td>[37]</td>
<td>Goserelin, RTOG 94–13</td>
<td>1295 randomized to 4 treatment arms: neoadjuvant goserelin + flutamide for 2 months before and during RT (whole pelvis [Arm 1] or prostate only [Arm 2]) or adjuvant goserelin + flutamide for 4 months after RT (whole pelvis [Arm 3] or prostate only [Arm 4])</td>
<td>5</td>
<td>No significant difference in 4-year PFS or overall survival in patients treated with neoadjuvant vs adjuvant therapy</td>
</tr>
</tbody>
</table>

*An additional two patients were randomized but found to be ineligible. EORTC, European Organization for the Research and Treatment of Cancer; ECOG, Eastern Cooperative Oncology Group; NS, not significant; RT, radiotherapy; RTOG, Radiation Therapy Oncology Group; RP, radical prostatectomy; PFS, progression-free survival; PSA, prostate-specific antigen.*
flutamide plus an LHRH agonist. There was no significant difference between groups in survival. Beyond this one comparative RCT, the currently available data relating to the efficacy of combined therapy shed no light on whether a class effect exists for antiandrogens.

**Tolerability**

The efficacy evidence is insufficient to show a class effect for the antiandrogens but there are differences between nonsteroidal antiandrogen monotherapies in terms of tolerability. Pharmacological effects associated with androgen receptor blockade, such as gynaecomastia and breast pain, have been reported with similar ranges of incidence for monotherapy with bicalutamide (38–66% and 13–73%, respectively), flutamide (21–80% and 22–69%, respectively) and nilutamide (gynaecomastia 50%, breast pain data not available) [40]. Gastrointestinal effects (e.g. diarrhoea) have also been reported with all three agents, but occur more often with flutamide than bicalutamide or nilutamide [40]. In contrast, visual disturbances and alcohol intolerance have been reported only with nilutamide [40]. There were also tolerability differences between treatments in the study by Schellhammer et al. [39]; e.g. the incidence of haematuria was significantly higher for the bicalutamide plus LHRH agonist group than for the flutamide plus LHRH agonist group (12% vs 6%, P = 0.007) and there was a significantly higher incidence of diarrhoea (26% vs 12%, P < 0.001) with flutamide than bicalutamide.

**Summary: antiandrogens**

Available efficacy data are insufficient to draw conclusions about the existence of a class effect for either steroidal or nonsteroidal antiandrogens. On the basis of tolerability data for nonsteroidal antiandrogens, it is clear that drugs in this class have different characteristics, suggesting that it is not appropriate to assume a class effect.

**CONCLUSIONS**

As outlined herein, there is a substantial amount of evidence that should be considered, together with clinical experience, so that urologists and their patients may make informed choices about the treatment of prostatic disease. It is clear that the issue is multifactorial and complex which, in addition to efficacy considerations, also encompasses differences between agents in safety/tolerability profiles. Although a class effect is commonly assumed in prostate medicine by some urologists, on the whole this is not supported by the evidence. For example, in the case of LHRH agonists, particularly for adjuvant therapy, the vast majority of data come from studies of goserelin. In contrast, there is less clinical evidence for other LHRH agonists in the adjuvant setting, because there are too few RCTs. This raises doubt as to whether a class effect for LHRH agonists is proven by existing clinical data across all stages of hormone-responsive prostate cancer. Similarly, a class effect has not been proven for other classes of agent that have been reviewed here. Urologists recognize the value of evidence-based practice, and on this basis, should not assume a class effect when making treatment choices for prostatic disease.

**CONFLICT OF INTEREST**

C. Evans is a paid consultant and study investigator funded by sponsor. N. Fleschner is a study investigator funded by sponsor. A.R. Zlotta is a paid consultant to sponsor. Source of funding: AstraZeneca.

**REFERENCES**

2. Evans CP. Evidence-based medicine for the urologist. BJU Int 2004; 94: 1–2
3. McAlister FA, Laupacis A, Wells GA, Sackett DL. Users’ guides to the medical literature. XIX. Applying clinical trial results B. Guidelines for determining whether a drug is exerting (more than) a class effect. JAMA 1999; 282: 1371–7


Correspondence: Christopher P. Evans, Department of Urology, University of California, Davis School of Medicine, 4860 Y St, Suite 3500, Sacramento CA 95817, USA. e-mail: christopher.evans@ucdavis.edu

Abbreviations: EBM, evidence-based medicine; RCT, randomized controlled trial; DES, diethylstilbestrol; CPA, cyproterone acetate.
Radical prostatectomy for clinically advanced (cT3) prostate cancer since the advent of prostate-specific antigen testing: 15-year outcome

JOHN F. WARD, JEFFREY M. SLEZAK*, MICHAEL L. BLUTE†, ERIK J. BERGSTRALH* and HORST ZINCKE†

Division of Urology, Naval Medical Center, Portsmouth, VA, *Division of Biostatistics, and †Department of Urology, Mayo Clinic, Rochester, MN, USA

Accepted for publication 2 December 2004

OBJECTIVE

To report a long-term experience with extirpative surgery in patients presenting with locally advanced (cT3) prostate cancer, as the best management of such patients remains a problem.

PATIENTS AND METHODS

In a single-institution retrospective study identifying 5652 men who had radical prostatectomy (RP) for histologically confirmed prostate cancer since the advent of prostate-specific antigen (PSA) testing (1987–97), 15% (842) had RP for cT3 disease. The median follow-up of these men was 10.3 years. Cancer-specific, overall and disease-free survival was plotted and compared with those of patients having RP for cT2 disease during the same period. Perioperative morbidity, continence and erectile function rates were examined, with a multivariate analysis for risk factors of disease recurrence.

RESULTS

Freedom from local or systemic disease at 5, 10, and 15 years after RP for cT3 disease was 85%, 73% and 67%; the respective cancer-specific survival rates were 95%, 90% and 79%. Significantly many men who did not receive neoadjuvant therapy (27%) were clinically over-staged (pT2) and most men with pT3 disease (78%) received adjuvant therapy. The mean time to adjuvant therapy after RP was not significantly different between men with cT3 and cT2 disease (4.0 and 4.3 years). Pathological grade (≥7), positive surgical margins, and nondiploid chromatin were all independently associated with a significant risk for clinical disease recurrence, while preoperative PSA level had little effect on outcome. Complications and continence rates after RP in patients with cT3 mirrored those in patients with cT2 disease.

CONCLUSIONS

Significantly many patients with cT3 prostate cancer are overstaged (pT2) in the PSA era. RP as part of a multimodal treatment strategy for patients with cT3 disease offers cancer control and survival rates approaching those achieved for cT2 disease. Pathological grade, ploidy and margin status are all significant predictors of outcome after RP. Complications and incontinence rates in patients with cT3 disease mirror those after RP for cT2 disease.

KEYWORDS

prostatic neoplasm, prostatectomy, treatment outcome, staging
INTRODUCTION

The presentational characteristics of prostate cancer have changed dramatically within the USA in the last few years, coincident with the widespread use of PSA testing as a screening tool. At our institution, where we have advocated radical prostatectomy (RP) for patients with cT3 prostate cancer for over 20 years [1,2], the proportion of RPs in men with cT3 disease has declined significantly, from 25.3% in 1987 to 2.8% in 2001 (Fig. 1). While we hope that stage migration in this period has accounted for much of this decline, lingering biases about the best management of cT3 disease may also be skewing the referral of such patients. It was reported that when the effect of upstaging in patients undergoing RP is excluded from the Surveillance, Epidemiology and End Results database, the number of those presenting with cT3 disease has remained remarkably stable for 20 years [3].

The best management of patients with clinically advanced prostate cancer remains controversial. At this stage the tumour appears to extend beyond the prostatic capsule, but distant metastases are not yet detectable. In the USA, surgery rates are 30% for patients with newly diagnosed cT1–2 disease, while only 6% of patients staged cT3 undergo RP [4]. Even in men with prolonged life-expectancy the RP rates are about 67% for the youngest with cT1–2 prostate cancer but only 19% for the youngest with cT3 disease [4]. Thus we present our retrospective single-institution experience with RP as primary therapy for patients with cT3 prostate cancer.

PATIENTS AND METHODS

Conduct of this study was approved by the Institutional Review Board (#1989–02) and constitutes a minimal-risk investigation. Consent for the use of medical records for research was obtained from all patients before starting this analysis. A single-institution retrospective study was conducted using the referral-based longitudinal Mayo Clinic Prostate Cancer Registry. Men (5662) who had RP with pelvic lymph node dissection during the 11-year (1987–97) period since the advent of PSA testing were identified. Clinical staging consisted of a digital rectal examination (DRE) by two clinicians, and defined using the 1997 American Joint Committee on Cancer guidelines. Bone scintigraphy, CT of the pelvis, and cystourethroscopy before RP was discretionary. No patient with confirmed distant metastasis underwent RP.

Locally advanced prostate cancer (cT3) with no distant metastasis, pelvic side-wall extension or involvement of the trigone was present in 841 (15%) of the identified patients. The clinical characteristics of all patients in the study period (cT2 and cT3) are presented in Table 1. There was a significant difference between these groups in preoperative PSA and biopsy grade. Neoadjuvant therapy was given to 23% and 5% of those staged cT2 and cT3, respectively.

The excised prostate glands were evaluated at the time of surgery by a standardized, limited-sampling protocol using frozen-section techniques. The following day the prostates were evaluated using haematoylin and eosin-stained permanent sections. The apex and base of the prostate were amputated and submitted as en fascia margins, followed by serial sectioning perpendicular to the long axis of the gland from apex to the tip of the seminal vesicles. On average, 14 prostate blocks were examined per patient. Pathological extraprostatic extension was defined as tumour extending into extraprostatic tissue (pT3). The primary tumour was graded according to the Gleason system. The lymph nodes were totally embedded for histological evaluation.

The median [range] follow-up was 10.3 (0.1–16.7) years. To date, adjuvant [≥90 days after RP] or salvage (>90 days after RP) therapies were administered to 48% and 41% of patients with cT3, and 21% and 22% of patients with cT2 disease.

Clinical progress was assessed at regular intervals either at our institution or by the referring physician, from the time of surgery throughout the follow-up. Clinical failure was defined as a serum PSA level of ≥0.4 ng/mL after RP, or demonstrable metastatic disease or local disease, or the initiation of salvage therapy [radiotherapy or hormonal therapy, HT] >90 days after RP. Disease outcome, perioperative and late treatment complications were retrieved by extensive record review and maintained within the registry.

The primary endpoints were times to death, prostate cancer death, clinical recurrence and biochemical failure (defined as a PSA of ≥0.4 ng/mL). Survival curves were generated using the method of Kaplan and Meier. Univariate and multivariate assessment of survival associations was conducted using the

![Clinical stage migration of 5652 newly diagnosed prostate cancers (T1c, green bars; T3-4, red) since the advent of PSA testing (1987–2001).](image-url)
log-rank test and Cox proportional hazard models.

RESULTS

The characteristics of the extirpated prostates are detailed in Table 2. Of the 661 men with cT3 disease who did not receive neoadjuvant HT, 27% were clinically over-staged, harbouring organ-confined prostate cancer (pT2). Nodal metastases (TxN+) were present in 27% of patients (37% after neoadjuvant HT, 27% without). The biopsy grade reviewed at the Mayo concurred with pathological grade in all but 6% of patients who had higher pathological grade disease. There was a significant difference in the chromatin content between patients with pT2 and pT3 disease (diploid, tetraploid, aneuploid, 71%, 22%, 7%, vs 51%, 35%, 14%, respectively).

Neoadjuvant HT was administered to 21% of patients (Table 2); rates of organ confinement (27%) and negative surgical margins (44%) were identical regardless of the preoperative administration of HT. Patients receiving neoadjuvant HT had a higher rate of pathological Gleason \( \geq 8 \) (25% vs 15%), N+ disease (37% vs 24%) and aneuploid DNA content (19% vs 12%) than patients not receiving HT.

The perioperative morbidity in patients with cT3 disease (Table 3) was similar to that previously reported for patients with cT2 disease undergoing RP at our institution [5]. There was a parallel decrease in hospitalized blood transfusions in patients with cT2 or cT3 over the study period. After RP, 75% of the reporting patients had no erectile function, reflecting the infrequent use of a nerve-sparing technique (12% bilateral, 14% unilateral nerve preservation, 74% wide excision of both neurovascular bundles) [6]. Urinary continence (completely dry or security pad seldom moist) at 1 year was achieved in 79% of men staged cT3 (84% cT2), with few (6%) patients having severe incontinence (\( \geq 2 \) pads/day) and 0.5% requiring an artificial urinary sphincter.

Of patients staged cT3 and cT2, 78% and 41% received HT, radiotherapy or both at some point after RP (Table 4). There was no significant difference in the time (mean, median) to initiate secondary therapy between cT3 (4.0, 3.5 years) and cT2 (4.3, 3.5 years).

At 5, 10 and 15 years after RP for cT3 disease, 85%, 73% and 67% of patients were free of local or systemic disease recurrence. Figure 2A compares this outcome with patients undergoing RP during the same period for cT2 disease. Freedom from biochemical recurrence for cT3 and cT2 at 5, 10 and 15 years had a similar relationship (58%, 43% and 38% for cT3, vs 74%, 61% and 52% for cT2). The overall (90%, 76%, 53%) and cancer-specific survival (CSS) (95%, 90%, 79%) for patients with cT3 disease at 5, 10 and 15 years was only moderately lower than that in patients with cT2 disease (95%, 82%).

### Table 2: Histological characterization of extirpated prostates for cT3 prostate cancer

<table>
<thead>
<tr>
<th>Group</th>
<th>All</th>
<th>HT before surgery, % (n)</th>
<th>Pathological stage (841)</th>
<th>Pathological Gleason score (738)</th>
<th>Chromosome content (816)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>pT2</td>
<td>pT3/4</td>
<td>TxN+</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>27 (223)</td>
<td>27 (174)</td>
<td>27 (49)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>46 (391)</td>
<td>49 (326)</td>
<td>36 (66)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>27 (227)</td>
<td>24 (161)</td>
<td>37 (66)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.064</td>
<td>0.037</td>
<td>0.022</td>
</tr>
</tbody>
</table>

### Table 3: Morbidity associated with RP in patients with cT3 disease

<table>
<thead>
<tr>
<th>Complication</th>
<th>Rate, % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectal injury</td>
<td>1.6 (14)</td>
</tr>
<tr>
<td>Intraoperative haemorrhage</td>
<td>1.8 (15)</td>
</tr>
<tr>
<td>Hospitalized blood transfusion</td>
<td>29.0 (241)</td>
</tr>
<tr>
<td>Hernia</td>
<td>2.6 (22)</td>
</tr>
<tr>
<td>Bladder neck contracture</td>
<td>11.2 (93)</td>
</tr>
<tr>
<td>Lymphocele</td>
<td>1.0 (8)</td>
</tr>
<tr>
<td>Urethral stricture</td>
<td>3.2 (27)</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>8.0 (16)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>1.2 (10)</td>
</tr>
<tr>
<td>Erectile dysfunction</td>
<td>75.3 (532 of 706 known)</td>
</tr>
</tbody>
</table>

### Table 4: Adjuvant and salvage therapies administered to patients with cT3 prostate cancer after RP, segregated by pathological stage

<table>
<thead>
<tr>
<th>Pathological stage (n)</th>
<th>HT, n (%)</th>
<th>Salvege†</th>
<th>Radiotherapy, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjuvant†</td>
<td></td>
<td>Adjuvant†</td>
</tr>
<tr>
<td>T2N0 (223)</td>
<td>64 (28.7)</td>
<td>40 (17.9)</td>
<td>24 (10.8)</td>
</tr>
<tr>
<td>T3/4N0 (391)</td>
<td>149 (38.1)</td>
<td>128 (32.7)</td>
<td>73 (18.7)</td>
</tr>
<tr>
<td>TxN+ (227)</td>
<td>216 (95.2)</td>
<td>51 (22.5)</td>
<td>36 (15.9)</td>
</tr>
<tr>
<td>Total (841)¶§</td>
<td>429 (51.0)</td>
<td>219 (26.0)</td>
<td>133 (15.8)</td>
</tr>
</tbody>
</table>

*1997 TNM Revision. †Adjuvant therapies were initiated \( \leq 90 \) days after RP. §Salvage therapies were initiated \( >90 \) days after RP. ¶5.2% of cT3 patients received both HT and radiotherapy at some time after RP. *13.2% of cT3 patients received adjunctive therapy before and after RP.
and 61%, and 99, 96% and 92%, respectively) during the same period (Fig. 2B). Stratified by pathological stage (Fig. 3), patients staged cT3 had a statistically significantly different CSS, but those staged pT3/4 had a 10- and 15-year CSS of 89% and 80% with adjuvant therapy.

The multivariate analysis of risk factors for clinical disease recurrence after RP for cT3 prostate cancer is shown in Table 5. Pathological grade (≥7), positive surgical margins and nondiploid chromatin content were all independently associated with a significant risk of clinical recurrence, while preoperative PSA level had little impact on this endpoint.

### DISCUSSION

Within this cohort of patients presenting to a single referral centre with cT3 prostate cancer, clinical over-staging occurred in a significant proportion of hormone-naive patients (27%); for these men, monotherapy with RP was potentially curative. Consistent with previous studies of the effect of neoadjuvant HT in patients with cT3 prostate cancer, HT given to 21% of the study cohort had little effect on grade, stage or rates of margin positivity, and did not influence progression-free or CSS. The morbidity of RP in these patients was no greater than that reported by us and others with RP for cT2 prostate cancer. However, the maintenance of erectile function was low in the present men (25% whose status was known), reflecting the wide resection of one or both neurovascular bundles in 88% of patients. Nonetheless, this erectile dysfunction rate compares favourably to those after RT for cT3 disease. For patients with cT3 disease, RP was part of a multimodal approach to disease eradication or control, which included HT or radiotherapy at some time after RP in 58% and 27%, respectively. Interestingly, the median time from surgery to secondary therapy for patients with cT3 disease was not significantly different from those with cT2. This probably reflects the biology of prostate cancer at the time of RP, regardless of clinical stage. As part of this multimodal approach to patients who once felt doomed to die from the disease, RP achieved CSS rates which approach those in patients with cT2 disease undergoing RP (90% vs 96% at 10 years and 79% vs 92% at 15 years).

This series represents the largest single-institution experience of the surgical management of cT3 prostate cancer, with a long-term follow-up (15 years) unmatched by any other therapy. Eliminating the prostate reduces the potential for late dissemination of radioresistant prostate cancer cells and simplifies the use of serum PSA levels in the follow-up. For a quarter of patients who are over-staged clinically, it eliminates the overtreatment of organ-confined disease with combined hormonal and radiotherapy, which is the current standard treatment for cT3 disease. With close follow-up and serial PSA measurements, the remaining patients harboring pT3 disease may avoid castration and the deleterious effect that this has on quality of life, until the PSA becomes detectable. On the other hand, patients with N+ disease, which unless bulky is difficult to detect with modern imaging techniques, can initiate early HT, which has been found to improve survival over delayed HT in patients with N+ disease [7].

Opponents of surgical treatment have cited a lack of benefit if the prostate is not completely excised [8], an increased incidence of micrometastasis [1], and increased surgical morbidity [9]. Wide-field irradiation has therefore become the standard accepted treatment. However, as a monotherapy, radiotherapy has had limited long-term success.

Prostate biopsy studies after radiotherapy showed persistent prostate cancer in 14–91% of patients [10,11]. Coen et al. [12] evaluated 1469 men with biopsy-confirmed prostate cancer treated with radiotherapy, and found not only an independent association between delayed metastasis and the local persistence of the cancer on biopsy, but also a temporally increasing hazard rate. They postulated that a biologically altered prostate cancer after radiotherapy resulted in a late wave of metastatic seeding, possibly worsening the outcome.

To improve the problem of local control with radiotherapy, radiotherapists have used a multimodal approach (radiotherapy and HT)

### TABLE 5 Multivariate analysis with hazard rates for clinical disease recurrence after RP in patients with cT3 prostate cancer (systemic or local disease)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathological grade ≥7</td>
<td>1.27 (1.03–1.56)</td>
<td>0.026</td>
</tr>
<tr>
<td>Pre-op PSA (doubling)</td>
<td>1.13 (0.96–1.34)</td>
<td>0.154</td>
</tr>
<tr>
<td>Ploidy (non-diploid)</td>
<td>1.85 (1.18–2.91)</td>
<td>0.008</td>
</tr>
<tr>
<td>Positive surgical margin</td>
<td>1.77 (1.12–2.79)</td>
<td>0.015</td>
</tr>
<tr>
<td>Seminal vesicle invasion</td>
<td>1.49 (0.92–2.43)</td>
<td>0.108</td>
</tr>
</tbody>
</table>

FIG. 2. A, The time free of local or systemic failure and B, CSS (segregated by clinical stage; cT2 green; cT3, red) after RP for patients with prostate cancer.

FIG. 3. The CSS for patients with cT3 disease segregated by final pathological stage (green solid line T2N0; red dotted line, T3–4N0, and light green dashed line, T4N+).
for treating cT3 prostate cancer. Lavérdière et al. [13] conducted a prospective study of patients with cT2-cT4 prostate cancer, randomly assigning patients to one of three treatment arms, i.e. radiotherapy alone, neoadjuvant HT and radiotherapy, or neoadjuvant HT + radiotherapy + adjuvant HT. As a monotherapy, radiotherapy inadequately controlled the cancer, with two-thirds of prostate biopsies 2 years after treatment positive for residual prostate cancer. However, with HT, the rate of positive biopsies improved to less than a third for neoadjuvant HT + radiotherapy, and <5% in the three-treatment arm.

Bolla et al. [14] conducted a prospective, randomized trial comparing radiotherapy alone vs radiotherapy + 3 years of adjuvant HT in men with advanced prostate cancer (367 cT3/cT4, 34 T1/T2 Grade 3, 14 N+). With a median follow-up of 5.5 years, the combined arm had better clinical disease-free (74% vs 40%) and overall survival (78% vs 62%, P < 0.001) than the radiotherapy-only arm. The clinical disease-free survival rate prospectively achieved for combined treatment compares with the 85% rate in the present retrospective study of RP and secondary therapy for cT3 disease.

Finally, the Radiation Therapy Oncology Group (RTOG 86–10) reported the results of a 15-year, prospective, randomized investigation of radiotherapy vs radiotherapy with 4 months of adjuvant HT in 471 men with cT3 prostate cancer (± lymph node involvement) [15]. At a median follow-up of 6.7 years, patients with Gleason score ≤6 prostate cancer receiving combined therapy had better local and distant disease control. However, there was no significant advantage to combined therapy (locoregional, distant metastasis or survival) in patients with Gleason 7–10 carcinomas. While the cancer grading for the RTOG study was based on a review of needle-biopsy specimens, we found a concordance between final pathological Gleason score and biopsy Gleason score in the present surgically treated patients (6% up-graded). With nearly two-thirds of the present patients with cT3 having Gleason ≥7 disease, the findings of RTOG 86–10 are worrisome.

The use and outcome of neoadjuvant HT followed by surgery has been examined prospectively but with significantly fewer patients than radiotherapy studies. The South-west Oncology Group (SWOG-9109) examined 55 patients staged cT3 who received 4-months of neoadjuvant total androgen blockade (goserelin + flutamide) with RP [16]. The 5-year progression-free and CSS estimate in this group, reported at a median follow-up of 6.1 years, was 70% and 90%, respectively. Similarly, Gleave et al. [17] found a 75% progression-free survival in such patients treated with 8-months of total androgen blockade followed by RP. Because of the infrequent use of neoadjuvant and frequent use of adjuvant HT within the present study we were unable to discern an effect of neoadjuvant HT. However, neoadjuvant HT did not affect the surgical margin status, which, with tumour ploidy, was the most significant predictor of clinical disease recurrence.

The optimum treatment strategy for high-risk/locally advanced prostate cancer remains unknown. However, definitive local treatments as monotherapy cure only a minority of patients in both radiotherapy and RP series. Multimodal therapy which includes androgen suppression and RP or radiotherapy clearly improves the outcome in men with locally advanced prostate cancer. Although the optimum timing of HT is not clear, short courses appear inferior to long-term therapy [18]. However, the effects of HT on quality of life are not insignificant. Over a quarter of the present men (pT2) would have been unnecessarily exposed to the adverse effects of HT if empirically treated. Another two-thirds of cT3 prostate cancers examined contained grade ≥7 cancer, a pattern for which radiotherapy ± HT regimens were less effective.

While HT has been the mainstay of combined therapy, recent efforts have focused on the delivery of chemotherapy and/or HT around RP. Koreny et al. [19] conducted a phase I/II study evaluating 36 patients with high-risk prostate cancer (cT3/A, cT1/B with Gleason 8–10 and/or PSA >20 ng/ml) who received neoadjuvant HT and four cycles of paclitaxel/carboplatin/estramustine before RP. Although the effect of this therapy on clinical progression-free survival is not yet known, the morbidity of such therapy was low and the positive surgical margin rate lower than in the present study (22% vs 56%).

The Cancer and Leukaemia Group B is conducting a prospective trial (CALGB-90203) comparing RP with estramustine and docetaxel before RP [20]. An ambitious accrual goal of 700 men during a 48-month period has been set. The primary study endpoint is a decrease in 3-year recurrence rates, with secondary outcomes comparing safety, tolerability and the impact of neoadjuvant therapy on the pathological specimen. Results of this study are not expected until after 2011.

While long-term progression-free and CSS is the ultimate goal of any treatment strategy, preventing the significant morbidity of local prostate cancer progression (bleeding, urethral/ureteric obstruction, pain) is also necessary. Within the present patients, none had any symptoms associated with local tumour recurrence or progression. Tomlinson et al. [21] assessed patients with newly diagnosed cT3 prostate cancer treated with either extirpative (perineal RP, 24) or less than extirpative surgery (TURP, 26) or simple RP (two). Non-extirpative surgery failed to ameliorate the local morbidity of in-situ tumour progression and 75% later developed BOO. Also, ureteric obstruction (40%), infection (80%) and gross haematuria (45%) were more frequent in the nonextirpative groups than in those patients undergoing RP (4%, 26%, and 9%, respectively).

Finally, a quarter of the present patients with cT3 were N+. We have long advocated the early introduction of HT for this stage of disease [7,22]. However, the ability to closely monitor serum PSA after RP for pT3 prostate cancer, with our increased awareness of the quality-of-life issues surrounding HT, means that we now closely observe patients with pT3N0 disease and initiate salvage therapy only after the patient has had a significant PSA doubling time after RP (<1 year) or clinical evidence of disease recurrence [23]. This is identical to our practice for patients with pT2N0 disease.

As presented here, the CSS and overall survival was excellent using this strategy in patients once considered incurable. However, this report has many limitations, beginning with its retrospective view, and an uncontrolled bias for the initiation and timing of adjuvant therapy before and/or after surgery. Second, as a tertiary centre, there was probably referral-pattern selection bias, which prevents an assessment of all men with newly diagnosed cT3 prostate cancer. Clinical trials comparing surgery or radiotherapy as part of a multimodal treatment regimen which
includes HT and/or chemotherapy are needed. Until then, the findings of this and other surgical series suggest that RP when combined with adjuvant HT compares favourably with current radiotherapy/HT strategies.

CONFLICT OF INTEREST

None declared.

REFERENCES

2 Lerner SE, Blute ML, Zincke H. Extended experience with radical prostatectomy for clinical stage T3 prostate cancer: outcome and contemporary morbidity. J Urol 1995; 154: 1447–52
8 Steinberg GD, Walsh PC. Expanding role in the management of patients with adenocarcinoma of the prostate. Problems Urol 1990; 4: 408–19

Correspondence: John F. Ward, 620 John Paul Jones Circle, Portsmouth, VA 23708, USA. e-mail: jfward@mar.med.navy.mil

Abbreviations: RP, radical prostatectomy; CSS, cancer-specific survival; HT, hormonal therapy; RTOG, Radiation Therapy Oncology Group.
The influence of bladder neck mucosal eversion and early urinary extravasation on patient outcome after radical retropubic prostatectomy: a prospective controlled trial

MIGUEL SROUGI, MARIO PARANHOS, KÁTIA M. LEITE, MARCOS DALL'OGLIO and LUCIANO NESRALLAH
Division of Urology, Federal University of São Paulo, São Paulo, Brazil
Accepted for publication 7 December 2004

OBJECTIVE
To evaluate the role of bladder neck (BN) mucosal eversion during retropubic radical prostatectomy (RRP) on the rate of BN sclerosis and urinary incontinence, with the hypothesis that BN mucosal eversion is not essential to improve the clinical outcome after RRP.

PATIENTS AND METHODS
One hundred patients with stage T1c–T2c prostate cancer had RRP by the same surgeon and were randomly divided in two equal groups; one had a vesico-urethral anastomosis with and one with no BN mucosal eversion. The patients were assessed by retrograde cysto-urethrography 4 days after surgery to evaluate the presence of urinary leakage. The occurrence of BN sclerosis and the rate of urinary incontinence after one pad/day was assessed by double-blind interviews at 2 days, 2 months and 6 months after catheter removal, and the incidence of BN sclerosis was also assessed after 12 months.

RESULTS
In the groups with or with no BN mucosal eversion, 48 and 47 patients, respectively, fulfilled the selection criteria. Urinary leakage after vesico-urethral anastomosis was more common after mucosal eversion (33% vs 21%), but not significantly (P = 0.251). BN sclerosis occurred in only one patient, with no mucosal eversion. The rate of urinary continence was similar in both groups at 2 days (69% vs 68%, respectively), 2 months (90% vs 87%) and 6 months (92% vs 92%) after surgery. Urinary extravasation at 4 days after surgery was followed by same rate of BN sclerosis and urinary continence as in patients with no urinary extravasation.

CONCLUSION
BN mucosal eversion before vesico-urethral anastomosis during RRP is not essential to reduce the frequency of BN sclerosis or urinary incontinence. Early radiological urinary extravasation at the vesico-urethral anastomosis did not increase the risk of BN sclerosis or urinary incontinence.

KEYWORDS
prostatectomy, surgical technique, urinary incontinence, bladder neck obstruction, stenosis.
All these data indicate that mucosal eversion in vesico-urethral anastomosis during RP might not be necessary, and it could even be deleterious if it increases the risks of urinary fistula and excessive local fibrosis. Thus we devised this study to determine if bladder mucosal eversion in RP is relevant to the outcome compared with the technique of vesico-urethral anastomosis with no mucosal eversion.

PATIENTS AND METHODS

In a randomized controlled study between October 2001 and June 2003 two groups of patients who had RP were compared; all patients gave informed consent, as approved by the Medical Ethics Committee of the Federal University of São Paulo. In all, 100 patients with T1 and T2 prostate cancer (median age 63 years, range 46–76) were recruited; patients were excluded if they had had: previous TURP, suprapubic prostatectomy or local radiotherapy; a history of neurological diseases; surgical pathology specimens that showed positive margins at the BN.

The participants were randomly assigned by computer into two equal groups undergoing RP with or with no bladder mucosal eversion before vesico-urethral reconstruction. All procedures were performed by the same surgeon (M.S.) who used a modified Walsh technique, with an attempt at bilateral nerve-sparing whenever feasible [13]. In patients having mucosal eversion, the bladder mucosa was pulled and attached to the external bladder surface with six circumferential sutures of 4/0 plain catgut (Fig. 1A). In both groups the BN was anastomosed directly to the urethra with eight 3/0 polyglactin interrupted sutures (Fig. 1B). The retropubic area was drained with a Penrose drain, and a urethral Foley catheter maintained in the bladder until 13 days after RP. All surgical specimens were evaluated histologically, according to a previous method and that included a careful examination of the surgical margins at the bladder neck [14].

At 4 days after RP all patients had retrograde cysto-urethrography with contrast medium injected around the Foley catheter under gravity; any contrast medium or extravasation at the vesico-urethral anastomosis was noted. At 48 h after removing the Foley catheter, and at 2 and 6 months after surgery, urinary continence was evaluated using a standard questionnaire, presented by an interviewer unaware of the treatment group (M.P.). Both groups were then compared for two primary endpoints, i.e. contrast medium extravasation at the anastomosis at 4 days after RP, and the rates of urinary continence and BN sclerosis at 48 h, 2 and 6 months after RP. The incidence of BN sclerosis was also assessed after a year. Those patients wearing more than one pad per day were classified as incontinent. At the same time, patients complaining of weak urinary stream had cysto-urethrography and cystoscopy to identify any BN sclerosis.

The chi-squared test was used to define uniformity between the groups, considering age, tumour stage, PSA level and Gleason score, and to compare the rates of contrast medium extravasation at 4 days. Fisher’s exact test was used to compare the frequency of BN sclerosis and urinary incontinence at 48 h, 2 and 6 months. In all tests, P > 0.05 was deemed to confirm the null hypothesis.

RESULTS

Among the patients recruited for the study, four were excluded as they were lost to follow-up and one was excluded after failing to undergo the radiological study 4 days after RP. For the final analysis the two groups included 48 (eversion) and 47 patients (no eversion), respectively. Table 1 shows the patient distribution for age, tumour stage, PSA level and Gleason score. The data show uniformity between the groups, considering age, tumour stage, PSA level and Gleason score, and to compare the rates of contrast medium extravasation at 4 days. Fisher’s exact test was used to compare the frequency of BN sclerosis and urinary incontinence at 48 h, 2 and 6 months. In all tests, P > 0.05 was deemed to confirm the null hypothesis.

Table 1 also shows the incidence of contrast medium extravasation at 4 days after RP; the rates of extravasation were similar for both groups (P = 0.251). Table 1 also compares both techniques for the frequency of BN sclerosis; there was no difference between the groups (P = 0.495). Table 1 also shows the rates of urinary continence at 48 h, 2 and 6 months after RP; the rates were similar in both groups (P = 0.856).

Table 2 shows the correlation between urinary extravasation and the occurrence of both BN sclerosis and urinary continence; extravasation had no effect on the occurrence of BN sclerosis, but there was a higher incidence of urinary incontinence at 48 h among patients with urinary extravasation, although the rates were the same at 2 and 6 months (P = 0.402).

DISCUSSION

To decrease the morbidity of retropubic RP, attempts have been made to refine the surgical technique [6,7], in the present study we assessed the issue of bladder mucosal eversion before vesico-urethral anastomosis. The outcome was similar for rates of BN sclerosis and urinary continence after vesico-urethral anastomosis with or with no mucosal eversion. Furthermore, there was a progressive improvement in urinary continence in both groups at the later follow-up. There was also a greater trend for urinary extravasation at 4 days after RP with mucosal eversion, although this was not statistically significant.

When the present study was designed we proposed that there might be a greater risk of urinary extravasation after BN reconstruction with mucosal eversion, a question raised after repeated observations in gastrointestinal surgery [9,12]. In patients undergoing enter-
The role of mucosal eversion during BN

Reviewing current reports we found none on initially suggested by Walsh [5]. Mucosal eversion, contrary to what was vesico-urethral reconstruction with no risk of extravasation of enteric contents. Enteric anastomosis, mucosal eversion can have a deleterious effect, as it increases the risk of extravasation of enteric contents. The same effect at the vesico-urethral anastomosis is unnecessary; this should reassure surgeons who perform laparoscopic RP, where this step is usually omitted [19]. Moreover, omitting this stage simplifies the procedure in open RP.

This prospective randomized study shows that it is possible to evaluate aspects of surgical technique with a sound scientific basis, contrary to what often occurs when surgical points are discussed empirically. We are convinced that other technical aspects of RP can be evaluated using similar trial designs, allowing advances in surgery and patient care based on a scientific rationale [13].

CONFLICT OF INTEREST

None declared.

REFERENCES


TABLE 1 Patient distribution for age, tumour stage, serum PSA, and Gleason score in both groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Eversion</th>
<th>No eversion</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>48</td>
<td>47</td>
<td>0.999</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;60</td>
<td>29</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td>19</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Clinical stage</td>
<td></td>
<td></td>
<td>0.535</td>
</tr>
<tr>
<td>T1</td>
<td>30</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>18</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Serum PSA, ng/mL</td>
<td></td>
<td></td>
<td>0.999</td>
</tr>
<tr>
<td>&lt;10</td>
<td>40</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>&gt;10</td>
<td>8</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Gleason score</td>
<td></td>
<td></td>
<td>0.102</td>
</tr>
<tr>
<td>2–6</td>
<td>19</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>7–10</td>
<td>29</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>N (%)</td>
<td></td>
<td></td>
<td>0.251</td>
</tr>
<tr>
<td>Urinary extravasation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>16 (33)</td>
<td>10 (21)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>32 (67)</td>
<td>37 (79)</td>
<td></td>
</tr>
<tr>
<td>BN sclerosis</td>
<td></td>
<td></td>
<td>0.495</td>
</tr>
<tr>
<td>Yes</td>
<td>0</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>48 (100)</td>
<td>46 (98)</td>
<td></td>
</tr>
<tr>
<td>Urinary continence at:</td>
<td></td>
<td></td>
<td>0.856</td>
</tr>
<tr>
<td>48 h</td>
<td>33 (69)</td>
<td>32 (68)</td>
<td></td>
</tr>
<tr>
<td>2 months</td>
<td>43 (90)</td>
<td>41 (87)</td>
<td></td>
</tr>
<tr>
<td>6 months</td>
<td>44 (92)</td>
<td>43 (92)</td>
<td></td>
</tr>
</tbody>
</table>

TABLE 2 Correlation between the presence of urinary extravasation and the rates of BN sclerosis and urinary continence

<table>
<thead>
<tr>
<th>Variable, n (%)</th>
<th>Urinary extravasation</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>N patients</td>
<td>26</td>
<td>69</td>
<td></td>
</tr>
<tr>
<td>BN sclerosis</td>
<td>2 months</td>
<td>26 (100)</td>
<td>68 (99)</td>
</tr>
<tr>
<td></td>
<td>6 months</td>
<td>0</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Urinary continence</td>
<td>48 h</td>
<td>14 (54)</td>
<td>51 (74)</td>
</tr>
<tr>
<td></td>
<td>2 months</td>
<td>23 (88)</td>
<td>61 (88)</td>
</tr>
<tr>
<td></td>
<td>6 months</td>
<td>24 (92)</td>
<td>61 (91)</td>
</tr>
</tbody>
</table>


Zhang Y, Glass A, Bennet N, Oyama KA, Gehan E, Gelmann EP. Long-term outcome after radical prostatectomy performed in a community based health maintenance organization. *Cancer* 2004; 100: 300–7


Correspondence: Miguel Srougi, Division of Urology, Federal University of São Paulo, Rua Peixoto Gomide, 2055/81, 01409-003 São Paulo, SP, Brazil. e-mail: srougi@terra.com.br

**Abbreviations:** RP, radical prostatectomy; BN, bladder neck.

**EDITORIAL COMMENT**

The authors are to be congratulated on their efforts to bring some science to the art of RP. Randomized studies are the only way to establish the truth behind the assertions of experienced surgeons, who tend to eulogise their particular way of accomplishing RP without subjecting their theories to rigorous testing. This study suggests that mucosal inversion may not reduce either anastomotic leakage or bladder neck contracture. However, there were relatively few patients, and when assessing a relatively uncommon complication like bladder neck contracture, a larger series of patients may be required. Another point is that the process of mucosal eversion may also help to achieve haemostasis at the bladder neck. Other important technical questions, e.g. the duration of urethral catheterization, and the pros and cons of laparoscopic and robotic approaches, also need to be assessed in a similar comparative manner in large series. It is to be hoped that this paper stimulates others to undertake such endeavours.

ROGER KIRBY
Prostate-specific antigen (PSA) complexed to α1-antichymotrypsin improves prostate cancer detection using total PSA in Japanese patients with total PSA levels of 2.0–4.0 ng/mL

TAKASHI KOBAYASHI, TOSHIYUKI KAMOTO*, KOJI NISHIZAWA, KENJI MITSUMORI, KEIJI OGURA and YOSHIHIRO IDE†
Departments of Urology and Surgical Pathology, Hamamatsu Rosai Hospital, Hamamatsu, and Urology, Kyoto University Graduate School of Medicine, Kyoto, Japan
Accepted for publication 8 November 2004
Presented in part at the 98th Annual Meeting of AUA, Chicago, Illinois, April 26–May 1, 2003

OBJECTIVE
To assess the utility of prostate-specific antigen (PSA) complexed to α1-antichymotrypsin (PSA-ACT) in prostate cancer screening in Japanese men with a total PSA level of 2.0–4.0 ng/mL, as improving cancer detection in men with these total PSA levels is a challenge for clinical urologists.

PATIENTS AND METHODS
Total PSA and PSA-ACT were prospectively assessed and prostate biopsy recommended for patients who met either of two thresholds, i.e. a total PSA of ≥2.0 ng/mL or a PSA-ACT of ≥1.5 ng/mL. The diagnostic ability of total PSA and PSA-ACT, and free-to-total PSA ratio and prostate volume-adjusted density were evaluated by receiver operating characteristic (ROC) analysis.

RESULTS
Of 1003 men enrolled, 547 met the biopsy criteria and a biopsy was taken in 315 (57.6%) patients. The area under the ROC curve for PSA-ACT (0.679) was significantly greater than that for total PSA (0.601, P = 0.04) and equivalent to that for the free-to-total ratio (0.686, P = 0.911) in 116 men, including 27 with cancer with total PSA levels of 2.0–4.0 ng/mL. PSA-ACT was more specific than the free-to-total ratio at a sensitivity of 95% (36% vs 18%, P < 0.05). The best variable for discriminating between cancer and benign disease in men with PSA levels of 2.0–4.0 ng/mL was PSA-ACT density (area under the curve 0.852) which provided 66% specificity at a sensitivity of 90%.

CONCLUSIONS
PSA-ACT is better than total PSA and equivalent to the free-to-total ratio for detecting prostate cancer in men with PSA levels of 2.0–4.0 ng/mL, and is thus useful for reducing the number of unnecessary biopsies.

KEYWORDS
PSA-ACT, diagnosis, prostatic adenocarcinoma, unnecessary biopsy, receiver operating characteristic analysis

INTRODUCTION
PSA is an extremely useful tumour marker, with a high sensitivity for the early detection of prostatic carcinoma and for the follow-up after treatment. Although using a low PSA threshold for prostate biopsy improves the treatment outcome [1,2], lowering the threshold results in more unnecessary biopsies.

Serum PSA occurs in several molecular forms, i.e. an unbound free form and complexed forms bound to α1-antichymotrypsin (PSA-ACT), α2-macroglobulin, protein C inhibitor, α1-antitrypsin, and inter-α-trypsin inhibitor [3,4]. Recent reports show that measuring some molecular forms, including PSA complexed to α1-protease inhibitor [5], complex PSA [6–8] and PSA-ACT [9,10], improve the discrimination of cancer from BPH in men with PSA levels of <10.0 ng/mL.

There have been a few studies on the utility of PSA-ACT for detecting prostate cancer in men with PSA levels of <4.0 ng/mL [11] but the utility of PSA-ACT in screening in Japanese men with total PSA levels of 2.0–4.0 ng/mL has yet to be elucidated. Herein we report a prospective study on the diagnostic ability of PSA-ACT compared with total PSA.

PATIENTS AND METHODS
The patients enrolled in the study were men aged ≤79 years who presented mainly for LUTS and were screened for prostate cancer between April 2001 and June 2003. The clinical evaluation comprised a measurement of prostate volume by TRUS, a DRE and serum PSA measurement. The three assays for total and free PSA and PSA-ACT were simultaneous on the same serum sample, which was obtained by venepuncture before manipulation of the prostate, then immediately frozen at −70°C and assessed prospectively within 3 days. Total and free PSA were quantified using the Tandem-R PSA Assay (Hybritech Inc., San Diego, CA), a solid-phase two-site immunoradiometric assay using two murine monoclonal antibody preparations specific for distinct sites on the PSA molecule. PSA-ACT was determined as described previously [12] with a two-site enzyme immunoassay (Markit-M, Dainippon Pharmaceutical Co. Ltd, Suita, Japan), in which standard PSA-ACT and its titre as PSA were adjusted by the Stanford reference [13].

A TRUS-guided prostatic needle biopsy was recommended in patients with either a total PSA level of ≥2.0 ng/mL or PSA-ACT of ≥1.5 ng/mL.
The diagnostic utility of PSA-associated variables for detecting cancer was evaluated using the area under (AUC) the receiver operating characteristic (ROC) curve, the curves being traced using appropriate software. All tests were two-sided and statistical significance was indicated at $P < 0.05$.

### RESULTS

During the 26-month period, 1003 Japanese men (mean age 67.1 years, SD 8.0, range 46–79) were enrolled in the study, and all had total and free PSA and PSA-ACT measured. There was a significant linear correlation between PSA-ACT and total PSA ($r = 0.96$; Fig. 1), whereas the correlation between total and free PSA was weak ($r = 0.24$; $0.131 < r < 0.380$). There were only seven (0.7%) cases in which the value of PSA-ACT was greater than that of total PSA.

Of the 1003 men, 544 (54.2%) and 506 (50.4%) met the threshold criteria of total PSA ≥ 4.0 ng/mL and PSA-ACT ≥ 0.88, respectively. Cancer was diagnosed in 105 of the 315 men (overall cancer detection rate 33%) and the cancer detection rate in the low and intermediate PSA groups was 23.3 (27 of 116) and 26.8% (37 of 138), respectively.

In the ROC analysis of the 116 patients in the low PSA group, the AUC for PSA-ACT was significantly larger than that for total PSA (Fig. 2A; Table 2), whereas there was no significant difference in the 138 of the intermediate and the 31 of the high PSA group (Fig. 2B,C). The proportional variables were comparable in both the low and intermediate PSA groups (Table 2). Sole use of PSA-ACT had an almost equivalent AUC to the combination of PSA-ACT and the difference from those of free PSA or PSA-ACT had an almost equivalent AUC to the combination of PSA-ACT and the difference from those of free PSA or total PSA density was not statistically significant (Table 2).

PSA-ACT gave significantly better specificities for avoiding an unnecessary biopsy than total PSA in the low-PSA group, whereas its ability was not significantly different from total PSA in the intermediate-PSA group (Table 2). At 95% sensitivity, the specificity of PSA-ACT was 36% compared with 18% for the free-to-total ratio ($P = 0.911$). Of all PSA-associated variables, PSA-ACT density was the strongest predictor in both the low and intermediate PSA groups, although the difference from total PSA density was not statistically significant (Table 2).

False-negative results from sampling error could influence the cancer detection rate, particularly in patients with a six-core biopsy. The cancer detection rate in the 46 patients who had six cores taken was 22%, compared with 24% in the remaining 70 assessed with a 10-core biopsy (Table 3; $P = 0.825$, Fisher’s exact test). These results may be explained by the difference in prostate volume of the patients in the two groups. The median prostate volumes were 30.4 mL in the six-core and 41.3 mL in the 10-core group ($P < 0.001$; Mann–Whitney $U$-test). In addition, although both total PSA and PSA-ACT were higher in the six-core than in the 10-core group, there was no significant difference in the proportion of PSA-ACT to total PSA (Table 3).

### DISCUSSION

Whether PSA-ACT is more useful for the early detection of cancer than variables associated with total PSA combined with free PSA or
prostate volume remains controversial [9,11,14–16]. In the present ROC analysis (Fig. 2) the AUC for PSA–ACT was significantly greater than that for total PSA in the low PSA group (Table 2). The tendency was similar in patients with a normal DRE, in which PSA–ACT gave an equivalent AUC to the combination of free and total PSA, it is possible that PSA–ACT may be more cost-effective, although this requires further study.

For men with an intermediate PSA level (4.1–10.0 ng/mL) there was no statistically significant difference between total PSA and PSA–ACT on ROC analyses, as reported previously [9,14–16]. There appears to be a growing consensus that PSA–ACT is slightly better than total PSA but not statistically significantly so in this PSA range. Free PSA may be important in explaining why the AUCs for PSA–ACT tend to be greater at lower PSA level. That the ratio of free PSA to PSA–ACT was greater at lower PSA levels indicates that free PSA has a greater effect on total PSA at lower PSA levels, resulting in PSA–ACT being more specific than total PSA, which is theoretically independent of the variation in free PSA that might be greater at lower PSA levels.

Some investigators have reported that early cancer detection with a low PSA level improves the positive surgical margin rate in radical prostatectomy [1] or lowers clinical stage, resulting in improved prognoses [2]. However, using a low PSA threshold for biopsy results in more unnecessary biopsies. Using PSA–ACT, the specificity improved from 25.8% to 40.4% at a sensitivity of 90%, and the number of biopsies required to detect one cancer decreased from 4 to 2.5 (Table 2). If a threshold for PSA–ACT of >1.7 ng/mL (at 90% sensitivity) had been applied, 36 of 105 biopsies would have been spared, whereas a threshold for total PSA of >2.4 ng/mL would not have been so effective, although this requires further study.

FIG. 2. Comparison of ROC curves between total PSA (green dashed line) and PSA–ACT (solid red line) at a total PSA of 2.0–4.0 (A), 4.1–10.0 (B) and ≥10.1 ng/mL (C) for discriminating prostate cancer from BPH. The line of equivalence is black.

TABLE 2 Specificities of PSA-associated variables related to sensitivity

<table>
<thead>
<tr>
<th>PSA group ng/mL [n]</th>
<th>Specificity [%] at sensitivity of (threshold)</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>95%</td>
<td>90%</td>
</tr>
<tr>
<td>2.0–4.0 (116)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total PSA</td>
<td>22.5(&gt;2.3)</td>
<td>25.8(&gt;2.4)</td>
</tr>
<tr>
<td>PSA–ACT</td>
<td>36.0(&gt;1.6)</td>
<td>40.4(&gt;1.7)</td>
</tr>
<tr>
<td>PSA–ACT/total PSA</td>
<td>38.2(&gt;0.595)</td>
<td>40.4(&gt;0.609)</td>
</tr>
<tr>
<td>Free/total PSA</td>
<td>18.0(&lt;0.292)</td>
<td>37.1(&lt;0.241)</td>
</tr>
<tr>
<td>Free/PSA–ACT</td>
<td>28.1(&lt;0.447)</td>
<td>31.5(&lt;0.428)</td>
</tr>
<tr>
<td>Total PSA density</td>
<td>43.8(&gt;0.071)</td>
<td>52.8(&gt;0.073)</td>
</tr>
<tr>
<td>PSA–ACT density</td>
<td>59.6(&gt;0.049)</td>
<td>66.3(&gt;0.053)</td>
</tr>
<tr>
<td>4.1–10.0 (138)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total PSA</td>
<td>7.9(&gt;4.2)</td>
<td>18.8(&gt;4.5)</td>
</tr>
<tr>
<td>PSA–ACT</td>
<td>8.9(&lt;2.7)</td>
<td>18.8(&lt;3.0)</td>
</tr>
<tr>
<td>PSA–ACT/total PSA</td>
<td>7.9(&gt;0.527)</td>
<td>28.7(&gt;0.609)</td>
</tr>
<tr>
<td>Free/total PSA</td>
<td>18.8(&lt;0.231)</td>
<td>37.6(&lt;0.196)</td>
</tr>
<tr>
<td>Free/PSA–ACT</td>
<td>27.7(&lt;0.344)</td>
<td>56.4(&lt;0.249)</td>
</tr>
<tr>
<td>Total PSA density</td>
<td>26.7(&gt;0.100)</td>
<td>32.7(&gt;0.105)</td>
</tr>
<tr>
<td>PSA–ACT density</td>
<td>19.8(&gt;0.057)</td>
<td>24.8(&gt;0.067)</td>
</tr>
<tr>
<td>≥10 (61)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total PSA</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>PSA–ACT</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

*P = 0.04. †P > 0.05.

FIG. 3. Changes in the ratio of free PSA to PSA–ACT in relation to the total PSA range. The ratio and the sensitivity (%) had been applied, 36 of 105 biopsies would have been spared, whereas a threshold for total PSA of >2.4 ng/mL would not have been so effective, although this requires further study.

TABLE 2 Specificities of PSA-associated variables related to sensitivity
have avoided only 25. Thus using only PSA-ACT was better than using the free-to-total ratio; the specificity of PSA-ACT was better than that of the free-to-total ratio both at 95% (38% vs 18%) and 90% (40% vs 37%) sensitivity. PSA-ACT density had the greatest AUC on ROC analysis (0.852, Table 2), similar to results in previous reports [9,10].

From the present study, for diagnosing prostate cancer in Japanese patients with serum PSA levels of 2.0–4.0 ng/mL, PSA-ACT is more specific than total PSA, and as specific as the free-to-total PSA ratio throughout the sensitivity range. PSA-ACT was more specific than free-to-total ratio at a sensitivity of 95%, around which the threshold values should be set.

For detecting prostate cancer in men with a low PSA level some authors have reported the usefulness of complexed PSA [17,18] or pro-enzyme PSA [19]. In these reports the PSA molecular forms improved cancer detection and were useful for sparing unnecessary biopsies. There have been few reports in which these new markers were directly compared. Unfortunately, other molecular forms of PSA were not measured in the current study and this remains for future research. According to recent studies on complexed PSA, and the present study, PSA-ACT seems to be as useful as complexed PSA in having a better specificity than total PSA and equivalent to the free-to-total PSA ratio [20].

There are some limitations of the present study. In retrospect, the predetermined thresholds for biopsy may be questionable. The total PSA threshold of 2.0 ng/mL seems very low, especially considering that the median age of the present men was 67 years. Although we attempted to enrol younger patients and considered the threshold of 2.0 ng/mL appropriate, the threshold should have been higher, or age-related thresholds used. Indeed, the cancer detection rate in men with PSA levels of 2.0–2.4 ng/mL was only 8% (two of 25). For PSA-ACT, although we determined the threshold of 1.5 ng/mL to be equivalent to that of total PSA based on a previous study [10], the present regression analysis predicted a PSA-ACT of 1.3 ng/mL at a total PSA of 2.0 ng/mL. As one of the aims of the study was to determine appropriate thresholds for biopsy, provisional values had to be a little lower, and the thresholds should be corrected appropriately as a result of the present study.

The number of biopsy cores was not constant in the present study, but the analysis in Table 3 suggests that it is less likely that the limited number of biopsy cores caused a significant bias for the difference between total PSA and PSA-ACT.

Another limitation is that patients with abnormal findings on DRE were included. However, the proportion of patients with such findings decreased with decreasing total PSA and PSA-ACT (Table 1). Indeed, at a PSA of 2.0–4.0 ng/mL, there were only three (2.6%) cases with an abnormal DRE, in which the biopsy results were all negative for cancer. Therefore, this issue seems to have less influence on the main aim of the study, to assess whether PSA-ACT is a good predictor for cancer detection in patients with PSA levels of 2.0–4.0 ng/mL.

The relatively low proportion of patients who had a biopsy of those who met the biopsy criteria could create a verification bias. The biopsy rate was 57.6% (315/547) overall and 45.8% (116/253) in men with total PSA levels of 2.0–4.0 ng/mL. Biopsy was uniformly recommended to all men who met the criteria in principle, and depended on the patient’s preference of whether to have a biopsy. There was no significant difference in median age (68 vs 70 years, P = 0.09, Mann–Whitney U-test) and free-to-total ratio (0.191 vs 0.185, P = 0.343) between men who had a biopsy and those who did not, whereas total PSA (3.1 vs 2.7 ng/mL, P < 0.001) and PSA-ACT (2.0 vs 1.8, P = 0.018) differed. This might result in a significant selection bias and is thus a limitation of the study.

In addition, the proportion of men with a total PSA level of >2.0 ng/mL was 54% (544/1003) and greater than expected in a prostate cancer screening programme. One possible explanation for this is that the patients were relatively older (median 69 years) than for a population being screened by PSA for prostate cancer. As noted above, the thresholds for biopsy were slightly too high in relation to age of the men. Another reason for the high proportion of men with a high PSA level is that they were referred with LUTS to a urological clinic. The median prostate volume was 40 mL (Table 1). For prostate cancer detection, men referred to urological clinics with LUTS should be considered as distinct from a screening population with no symptoms; they have a higher PSA level, larger prostates and higher cancer incidence [21]. Therefore, the results of the present study should not be directly translated into an extensive screening programme for prostate cancer in which the subjects would be younger men with no LUTS, and further studies are warranted. However, PSA-ACT seems to be promising in that it is more useful in men with a low PSA level than conventional total PSA, and has high specificity.

**Table 3 Total PSA and PSA-ACT in 1003 patients**

<table>
<thead>
<tr>
<th>Median (range)</th>
<th>Biopsy cores</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>N</td>
<td>46</td>
<td>70</td>
</tr>
<tr>
<td>Total PSA, ng/mL</td>
<td>3.2 (2.1–4.0)</td>
<td>2.9 (2.0–4.0)</td>
</tr>
<tr>
<td>PSA-ACT, ng/mL</td>
<td>2.2 (1.1–3.3)</td>
<td>1.8 (1.0–3.5)</td>
</tr>
<tr>
<td>ACT/total ratio</td>
<td>0.667 (0.393–0.914)</td>
<td>0.680 (0.462–0.90)</td>
</tr>
<tr>
<td>Prostate volume, mL</td>
<td>30.4 (13.9–49.0)</td>
<td>41.3 (16.7–98.6)</td>
</tr>
<tr>
<td>Cancer detection rate, %</td>
<td>21.7</td>
<td>24.3</td>
</tr>
</tbody>
</table>

**ACKNOWLEDGEMENTS**

The authors thank Dainippon Pharmaceutical Co. Ltd, Suita, Osaka, Japan, for laboratory assistance. This study was funded by a medical research grant from the Japanese Labour Welfare Corporation, 2002.

**CONFLICT OF INTEREST**


**REFERENCES**

1. Berger AP, Volgger H, Rogatsch H et al. Screening with low PSA cutoff values

KOBAYASHI ET AL.
results in low rates of positive surgical margins in radical prostatectomy specimens. *Prostate* 2002; 53: 241–5


10 Kobayashi T, Kamoto T, Isogawa Y et al. Ratio of prostate specific antigen minor molecular forms to total prostate specific antigen is constant regardless of the pathological condition of the prostate. *J Urol* 2003; 169: 121–4


14 Jung K, Brux B, Lein M et al. Determination of alpha 1-antichymotrypsin-PSA complex in serum does not improve the differentiation between benign prostatic hyperplasia and prostate cancer compared with total PSA and percent free PSA. *Urology* 1999; 53: 1160–7


19 Sokoll LJ, Chan DW, Mikolajczyk SD et al. Proenzyme PSA for the early detection of prostate cancer in the 2.5–4.0 ng/ml total PSA range: preliminary analysis. *Urology* 2003; 61: 274–6


Correspondence: Takashi Kobayashi, Department of Urology, Hamamatsu Rosai Hospital, Shogen-cho 25, Hamamatsu, Japan, 430–8525. e-mail: selecao@remus.dti.ne.jp

Abbreviations: ACT, alpha-1-antichymotrypsin; ROC, receiver operating characteristic (curve); AUC, area under the curve.
A novel technique for approaching the endopelvic fascia in retropubic radical prostatectomy, based on an anatomical study of fixed and fresh cadavers

ATSUSHI TAKENAKA, RYOEI HARA, HIDEO SOGA*, GEN MURAKAMI† and MASATO FUJISAWA

Departments of Urology, Kawasaki Medical School and *Kawachi General Hospital, and †Department of Anatomy, Sapporo Medical University School of Medicine, Japan

Accepted for publication 29 November 2004

OBJECTIVE

To present the anatomical basis and details of a technique for an approach to the endopelvic fascia devised to preserve urinary continence.

PATIENTS, MATERIALS AND METHODS

For cross-sectional macroscopic observation, seven formalin-fixed specimens of the male pelvic contents including the pelvic wall were serially sectioned at a 5-mm thickness. Semi-seral sections from eight other specimens were examined histologically. Eight fresh cadavers were dissected to mimic the various steps in a retropubic radical prostatectomy. After approaching the endopelvic fascia in an anatomically determined manner to reach the paraprostatic space, the pubic bone was removed and nerves near the rhabdosphincter dissected. To assess the clinical implication of this approach, we examined the time to achieve continence in 23 consecutive patients who had a radical retropubic prostatectomy using the new technique.

RESULTS

Sectional macroscopic observation depicted the fascia of the levator ani as a definite structure adherent to but not fused with the lateral pelvic fascia. The thin fascia overlying the levator ani fascia and lateral pelvic fascia represented the true endopelvic fascia. Microscopically, the lower part of the fascia of the levator ani was rich in smooth muscle, which interdigitated with the framework of the rhabdosphincter. In fresh cadavers, the levator ani muscle was removed laterally still covered by its fascia, without visualizing the muscle fibres. Small branches from the pudendal nerve entered the rhabdosphincter. The mean (SD, range) distance from the lowest point of the endopelvic fascia to the point where the sphincteric branch entered the rhabdosphincter was 5.5 (1.8, 3–8) mm. The continence rate at 1, 3, 6 and 9 months after surgery using the new technique was 44%, 83%, 96% and 100%, respectively.

CONCLUSIONS

Preserving the fascia of the levator ani helps to protect the levator ani muscle, rhabdosphincter and pudendal nerve branches to the rhabdosphincter. In retropubic radical prostatectomy, this anatomical approach to the endopelvic fascia should preserve or allow the earlier recovery of urinary continence.

KEYWORDS
endopelvic fascia, fresh cadaver, urinary incontinence
ANATOMICAL APPROACH TO ENDOPELVIC FASCIA

© 2005 BJU INTERNATIONAL

and eosin staining or immunohistochemical staining as described previously by Murakami et al. [5] was used. The primary antibody used in the immunohistochemical evaluation was monoclonal antihuman α-smooth muscle actin (mouse IgG2a, κ; Dako, Kyoto, Japan).

In the eight fresh cadavers, dissections were sequential to mimic the various steps in retropubic RP leading up to exposure of the apex of the prostate. The mean age at death for these specimens was 78 (71–88) years. The cadavers had been donated to Sapporo Medical University within 24 h of death. No fixatives were used, and hemicorporectomy and femoral abscission were performed. The cadavers were maintained at −20°C, and before dissection were thawed gradually to minimize tissue damage. The dissection was carried out using an operating microscope (¥2.5, Surgical Acuity, Meddleton, WI). The abdominal wall, small intestine and sigmoid colon were removed, leaving the rectum intact. The cadavers were maintained at −20°C, and before dissection were thawed gradually to minimize tissue damage. The dissection was carried out using an operating microscope (¥2.5, Surgical Acuity, Meddleton, WI). The abdominal wall, small intestine and sigmoid colon were removed, leaving the rectum intact. After widening the prevesical space and removing the prevesical fat, the EPF was exposed. After this anatomical approach to the EPF, to reach the paraprostatic space, the deep dorsal vein complex was gathered together and the apex of the prostate exposed. The pubic bone was then removed and the nerves near the rhabdosphincter dissected.

For the clinical study, 23 patients with clinically localized (T1-2N0M0) prostate cancer had a retropubic RP using the new technique for approaching the EPF. To avoid positive margins we included in this pilot study only patients with a PSA level of <20 ng/mL and biopsy specimens that did not contain Gleason grade 5 disease. The patients had a mean (SD) age of 68.2 (4.8) years, PSA level of 11.2 (6.4) ng/mL and a mean follow-up of 13.5 (2.3) months. The urinary catheter was removed 1–3 weeks after surgery. Patients who did not use incontinence pads were defined as continent. Interviews were conducted at regular intervals until the patient reported being completely continent.

RESULTS

By sectional macroscopic observation we identified the levator ani (LA) muscle and the fascia of the LA (FLA) in frontal and axial sections. Frontal sections along the membranous urethra in formalin-fixed cadavers showed the FLA as a well-defined structure adhering to the prostate-urethral junction. A frontal section along the membranous urethra shows the FLA as a well-defined structure adhering to the prostate-urethral junction. B: In an axial section from another formalin-fixed specimen, the FLA on the right side was not attached to the LPF; thin fascia connected the FLA and the LPF. We think that this thin layer is the EPF. The FLA on the left side was attached to the LPF, and there was a space between the FLA and the LA muscle. Black and white arrow, the FLA; black arrowhead, LPF; black star, junction of the FLA and the membranous urethra; white star, EPF; asterisk, space between the FLA and the LPF; #, space between the FLA and the LA; PR, prostate; UR, urethra; REC, rectum.

FIG. 1. Macroscopic findings in the area of the EPF and FLA. A: The LA, FLA and the apex of the prostate in a formalin-fixed cadaver. A frontal section along the membranous urethra shows the FLA as a well-defined structure adhering to the prostate-urethral junction. B: In an axial section from another formalin-fixed specimen, the FLA on the right side was not attached to the LPF; thin fascia connected the FLA and the LPF. We think that this thin layer is the EPF. The FLA on the left side was attached to the LPF, and there was a space between the FLA and the LA muscle. Black and white arrow, the FLA; black arrowhead, LPF; black star, junction of the FLA and the membranous urethra; white star, EPF; asterisk, space between the FLA and the LPF; #, space between the FLA and the LA; PR, prostate; UR, urethra; REC, rectum.

and eosin staining or immunohistochemical staining as described previously by Murakami et al. [5] was used. The primary antibody used in the immunohistochemical evaluation was monoclonal antihuman α-smooth muscle actin (mouse IgG2a, κ; Dako, Kyoto, Japan).

In the eight fresh cadavers, dissections were sequential to mimic the various steps in retropubic RP leading up to exposure of the apex of the prostate. The mean age at death for these specimens was 78 (71–88) years. The cadavers had been donated to Sapporo Medical University within 24 h of death. No fixatives were used, and hemicorporectomy and femoral abscission were performed. The cadavers were maintained at −20°C, and before dissection were thawed gradually to minimize tissue damage. The dissection was carried out using an operating microscope (¥2.5, Surgical Acuity, Meddleton, WI). The abdominal wall, small intestine and sigmoid colon were removed, leaving the rectum intact. After widening the prevesical space and removing the prevesical fat, the EPF was exposed. After this anatomical approach to the EPF, to reach the paraprostatic space, the deep dorsal vein complex was gathered together and the apex of the prostate exposed. The pubic bone was then removed and the nerves near the rhabdosphincter dissected.

For the clinical study, 23 patients with clinically localized (T1-2N0M0) prostate cancer had a retropubic RP using the new technique for approaching the EPF. To avoid positive margins we included in this pilot study only patients with a PSA level of <20 ng/mL and biopsy specimens that did not contain Gleason grade 5 disease. The patients had a mean (SD) age of 68.2 (4.8) years, PSA level of 11.2 (6.4) ng/mL and a mean follow-up of 13.5 (2.3) months. The urinary catheter was removed 1–3 weeks after surgery. Patients who did not use incontinence pads were defined as continent. Interviews were conducted at regular intervals until the patient reported being completely continent.

RESULTS

By sectional macroscopic observation we identified the levator ani (LA) muscle and the fascia of the LA (FLA) in frontal and axial sections. Frontal sections along the membranous urethra in formalin-fixed cadavers showed the FLA as a well-defined structure adhering to the prostate-urethral junction. A frontal section along the membranous urethra shows the FLA as a well-defined structure adhering to the prostate-urethral junction. B: In an axial section from another formalin-fixed specimen, the FLA on the right side was not attached to the LPF; thin fascia connected the FLA and the LPF. We think that this thin layer is the EPF. The FLA on the left side was attached to the LPF, and there was a space between the FLA and the LA muscle. Black and white arrow, the FLA; black arrowhead, LPF; black star, junction of the FLA and the membranous urethra; white star, EPF; asterisk, space between the FLA and the LPF; #, space between the FLA and the LA; PR, prostate; UR, urethra; REC, rectum.

FIG. 1. Macroscopic findings in the area of the EPF and FLA. A: The LA, FLA and the apex of the prostate in a formalin-fixed cadaver. A frontal section along the membranous urethra shows the FLA as a well-defined structure adhering to the prostate-urethral junction. B: In an axial section from another formalin-fixed specimen, the FLA on the right side was not attached to the LPF; thin fascia connected the FLA and the LPF. We think that this thin layer is the EPF. The FLA on the left side was attached to the LPF, and there was a space between the FLA and the LA muscle. Black and white arrow, the FLA; black arrowhead, LPF; black star, junction of the FLA and the membranous urethra; white star, EPF; asterisk, space between the FLA and the LPF; #, space between the FLA and the LA; PR, prostate; UR, urethra; REC, rectum.
Removal of the pubic bone identified the FLA as the plate forming the pelvic floor, with the FLA bordering intrapelvic and infrapelvic regions (Fig. 2E). This procedure was completed in six of eight specimens; in the other two, when we tried to remove the LA laterally, the FLA was fused with the LPF near the apex of the prostate. In these specimens the prostate-urethral junction was reached after exposing the LA muscle fibres. Small branches from the pudendal nerve reached the rhabdosphincter in all fresh cadavers (Fig. 3); these represented the sphincteric branch of the pudendal nerve. This branch was anterolateral to the rhabdosphincter. The mean (so, range) distance from the lowest point of the FLA to the point where the nerve branch entered the rhabdosphincter was 5.5 (1.8, 3–8) mm. After exposing the LA fibres beneath the FLA, the distance between the pelvic floor and the nerve entry point decreased. The defect created in the FLA rendered this nerve vulnerable to injury. After giving rise to this branch, the pudendal nerve coursed to the penile hilum to become the dorsal nerve of the penis.

Microscopically, the FLA was thick and covered the inferomedial margin of the LA, bordering intrapelvic and infrapelvic regions. The FLA did not appear strongly adherent to the prostate, differing from the impression obtained by macroscopic observation, and appearing somewhat counter to the surgical practice of many urologists who leave the FLA on the visceral surface. The FLA overlying the lower inner corner of the LA radiated to the framework of the rhabdosphincter (Fig. 4A). Staining with anti-smooth muscle actin indicated that the lower part of FLA was rich in smooth muscle, and that this component interdigitated with the rhabdosphincter (Fig. 4B). In two of the eight specimens examined histologically, many vessels were interposed between the FLA and LPF or situated under the LPF (Fig. 4C). In these specimens, excessive bleeding would have resulted unless the prostate-urethral junction was reached by exposing the LA muscle fibres.

In the clinical study, all 23 men regained continence, attained immediately after catheter removal in three (13%), within 1 week in eight (35%), and within 1, 3, 6 and 9 months in 10 (44%), 19 (83%), 22 (96%) and all, respectively.

**DISCUSSION**

Textbooks on urological surgery describing retropubic RP direct urologists to incise the so-called EPF to reach the paraprostatic space. Generally, the ‘EPF’ is thought to refer to the fascia in the transitional area between the pelvic wall and pelvic viscera. Many descriptions not based on anatomical study resemble one that reads, ‘After the EPF is incised just lateral to the white line, bare levator muscle fibres are viewed, which then are displaced bluntly and laterally from the lateral surfaces of prostate and rectum’ [6]. In these accounts, the existence and
implications of the FLA are not considered. When we reviewed anatomically based reports of the EPF the term was used in two different senses. One meaning used by Steiner [7] referred to the parietal fascia lateral to the so-called arcus tendineus fascia pelvis, distinguishing the EPF from the FLA. On the other hand, Myers [2] equated the EPF with the FLA. We think that the intrapelvic fascial anatomy has not been fully elucidated, and that the terminology is inconsistent.

Figures in anatomical textbooks [8,9] tend to show the FLA as a very thick membrane not attached to the LPF, while the parietal pelvic fascia is not shown. Anatomists who work with formalin-fixed cadavers and have not performed surgery use the term ‘EPF’ in the same sense as ‘FLA’, and cannot understand references to ‘incision of the EPF’. We think that the anatomical discrepancy between observations from surgical and formalin-fixed cadavers has resulted in confusion about the FLA. Steiner [7] and Myers [2], who almost always used fresh cadavers for anatomical studies, recognized the existence of the FLA. The present sectional macroscopic observations in formalin-preserved cadavers sharply contrasted the thick FLA and the thin parietal pelvic fascia, as being distinctly different structures (Fig. 5). While we support Steiner’s opinion, the approach to the paraprostatic space has not been described in detail. In ordinary practice, surgeons who recognize the existence of the FLA and those who do not, incise two fascial planes, the parietal pelvic fascia and the FLA, when they believe that they are incising the EPF.

We used the term ‘EPF’ to refer to the parietal and visceral pelvic fascia, similar to Steiner [7], but we approached them by a slightly different method (Fig. 5). In the fresh-cadaver study, we incised the thin parietal and visceral pelvic fascia just medial to the attachment point of the FLA, and removed the LA laterally while covered by the FLA, without visualizing the muscle fibres. This point sometimes was anterolateral rather than lateral to the prostate side. Conventionally, the incision could be made just lateral to this point (i.e. the arcus tendineus pelvic fascia). Thus, we advocate a new approach to the EPF based on anatomical study of both formalin-fixed and fresh cadavers. However, the new approach cannot be applied to all cases; we encountered some specimens where the FLA fused with the LPF near the apex of the prostate, or where many vessels coursed between the FLA and LPF or under the LPF. In such cases, the approach between FLA and LA must be changed to avoid excessive blood loss.

Many recent studies have discussed the neuroanatomy of the rhabdosphincter. Hollabaugh et al. [10] reported that both the pelvic and pudendal nerves supplied intrapelvic branches that coursed bilaterally, entering the external sphincter at the 5 and 7 o’clock positions. Narayan et al. [11] measured the distance from the prostate apex to the point of nearest pudendal branch entry into the sphincter as 3.2–12.7 mm, similar to the present results (3–8 mm). While variable, this distance sometimes was very short (Fig. 3), indicating that surgeons must be very careful manipulating in the prostatic apex and its interface with the LA so as not to injure the nerve branch to the rhabdosphincter. The present new approach to the EPF should prove very useful in this regard.

The LA is considered to be important in continence mechanisms [12]. Murakami et al. [5] described the rhabdosphincter as acting not only as a sphincter but also as a retractor, levator, or force transmitter with the aid of the LA. The present immunostaining finding, that smooth muscle tissue in the lower part of the FLA interfused with the rhabdosphincter, supports this hypothesis. In terms of innervation, Juennemann et al. [13] suggested that the rhabdosphincter and LA formed a functional complex. Interestingly, Nelson et al. [14] described intraoperative electrical stimulation of the neurovascular bundle causing an increase in urethral pressure, functionally identifying the intrapelvic neural pathway that innervated the male sphincter. An additional increase in urethral pressure upon pelvic wall stimulation represented technical failure, but the result nonetheless emphasises the significance of
However, it is evident from our anatomical
study that the new approach does not lead to
more positive margins than the usual nerve-
sparing approach [22].

In conclusion, this anatomical study of the
EPF led us to a new surgical approach to the
EPF. The area under the FLA just lateral to the
prostatic apex and the sphincter should be
considered important for urinary continence.
In retropubic RP, this new approach should
facilitate preservation or early recovery of
urinary continence, as preserving the FLA
leads to protection of the LA and the
rhabdosphincter, as well as avoiding
the pudendal nerve branch to the
rhabdosphincter.

CONFLICT OF INTEREST
None declared.

REFERENCES
1 Walsh PC. Anatomic radical retropubic
prostatectomy. In Walsh PC, Retik AB,
Vaughan ED, Wein AJ eds. Campbell’s
Urology, 8th edn. Philadelphia: WB
Saunders, 2002; 3107–29
2 Myers RP. Radical prostatectomy:

There are conflicting reports on the risk
factors for urinary incontinence after RP, e.g.
patient age, preoperative continence status,
previous TURP, anastomotic stricture, stage of
disease and, of course, surgical technique and
the experience of the surgeon. Applying this
new technique in the present pilot study led
to a good continence rate and a rapid return
of urinary control. The present continence
results are better than in other recent reports
from large series [16–20], where continence
rates were 88.8–99.5%. In the present study,
83% of patients were continent at 3 months,
which compares favourably with a report by
Eastham et al. [21], where 75% of patients
were continent at 4 months.

Currently we cannot comment on whether
the new surgical procedure causes more
positive surgical margins because we limited
patients in this pilot study to those who were
strongly predicted to have localized tumours.
However, it is evident from our anatomical
disease and, of course, surgical technique and
the experience of the surgeon. Applying this
new technique in the present pilot study led
to a good continence rate and a rapid return
of urinary control. The present continence
results are better than in other recent reports
from large series [16–20], where continence
rates were 88.8–99.5%. In the present study,
83% of patients were continent at 3 months,
which compares favourably with a report by
Eastham et al. [21], where 75% of patients
were continent at 4 months.

Currently we cannot comment on whether
the new surgical procedure causes more
positive surgical margins because we limited
patients in this pilot study to those who were
strongly predicted to have localized tumours.
However, it is evident from our anatomical

Pertinent surgical anatomy. Atlas Urol Clin
North Am 1994; 2: 1–18
3 Myers RP. Practical surgical anatomy for
radical prostatectomy. Urol Clin North Am
2001; 28: 473–90
4 Takenaka A, Murakami G, Soga H, Han
SH, Arai Y, Fujisawa M. Anatomical
analysis of the neurovascular bundle
supplying penile cavernous tissue to
ensure a reliable nerve graft after
radical prostatectomy. J Urol 2004;
172: 1032–5
5 Murakami G, Nakajima F, Sato TJ,
Tsugane MH, Taguchi K, Tsukamoto T.
Individual variations in aging of the male
urethral rhabdosphincter in Japanese. Clin
6 Bartsch G, Poisel S eds. Approaches in
Urologic Surgery. New York: Thieme
7 Steiner MS. Continence-preserving
anatomic radical retropubic
8 Kopf–Maier P. Atlas of Human Anatomy,
262
9 Putz R, Paist R. Atlas of Human
Lippincott, Williams & Wilkins 2001; 132–
261
10 Hollabaugh RS Jr, Dmochowski RR,
Steiner MS. Neuroanatomy of the male
11 Narayan P, Koney B, Aslam K, Aboseif

FIG. 4. Configurations of the FLA. A: Microscopic findings (frontal section through urethra) of the FLA near the
apex of the prostate (haematoxylin and eosin). The FLA is thick and covers the inferomedial margin of the LA,
radiating to the framework of rhabdosphincter over the lower inner corner of the LA. B: High magnification
of staining with anti-smooth muscle actin, corresponding to the square in panel A. The FLA was rich in
smooth muscle; this component interdigitated with the rhabdosphincter.

FIG. 5. Scheme of the fascial anatomy in the area
around the prostate. Almost all urologists approach the
paraprostatic space on the line indicated by the
solid arrow. The new anatomical approach (line with
dotted arrow) might be a better alternative in many
cases.

© 2005 BJU INTERNATIONAL
ANATOMICAL APPROACH TO ENDOPELVIC FASCIA


Correspondence: Atsushi Takenaka, Department of Urology, Kawasaki Medical School, 577 Matsushima, Kurashiki, 701–0192, Japan.
e-mail: atake@med.kawasaki-m.ac.jp

Abbreviations: EPF, endopelvic fascia; LA, levator ani; FLA, fascia of the levator ani; LPF, the lateral pelvic fascia; RP, radical prostatectomy.
The incidence and treatment of lymphoceles after radical retropubic prostatectomy

RUTH J. PEPPER, JHUMUR PATI and AMIR V. KAISARY
Department of Urology, Royal Free Hospital, London, UK
Accepted for publication 9 November 2004

OBJECTIVE
To determine the incidence and treatment of lymphoceles after radical retropubic radical prostatectomy (RP).

PATIENTS AND METHODS
Up to January 2004, 260 patients who had a retropubic RP in one institution by one surgeon were assessed retrospectively, using the patients' notes or the computerized results system to determine whether a lymphocele was suspected and then confirmed by imaging studies (computed tomography or ultrasonography).

RESULTS
Nine patients developed symptomatic lymphoceles; eight of these were detected by imaging. Four lymphoceles required intervention while the remainder regressed spontaneously. No complications were reported in the group that was treated.

INTRODUCTION
A lymphocele, also known as a lymphocyst, is a collection of lymphatic fluid occurring as a consequence of surgical dissection and inadequate closure of afferent lymphatic vessels. It is an uncommon although well documented complication after renal transplantation or pelvic surgery. A large study of 1243 patients [1] treated by radical prostatectomy (RP) showed that 75 had a lymphocele afterward, an incidence of 6%; 2.3% of these were minor lymphoceles and were drained under ultrasonographic guidance, with only eight patients (0.6%) requiring CT-guided drainage or marsupialization. In the remaining 3.1% the lymphoceles were considered a minor complication, which resolved spontaneously and required no intervention.

Ultrasonography (US) and occasionally CT are used to diagnose lymphoceles, as well as cytological and biochemical analysis of the aspirate, which can be used to aid in their diagnosis. The incidence of clinically detected lymphoceles in laparoscopic pelvic lymph node dissection has been reported to be as low as 1%, and lower than the 4.7–14.8% after open pelvic lymph node dissection [2].

The aim of the present study was to determine the incidence of lymphoceles after retropubic RP and determine the best method of diagnosis and treatment.

PATIENTS AND METHODS
In this retrospective study, 260 patients had retropubic RP for localized prostatic carcinoma by one surgeon, up to January 2004. The operative approach was through a lower midline incision, followed by bilateral internal iliac pelvic nodal clearance along the iliac vessels, up to the level of the obturator nerve inferiorly and including the lymph node of Cloquet laterally. All patients received perioperative antibiotics and had a pelvic drain placed after RP.

The patients' notes or the computerized results system were examined to determine whether a lymphocele was suspected and then confirmed by imaging studies (CT or US).

RESULTS
Nine patients developed symptomatic lymphoceles, which were apparent at 12–120 days after RP. The main presenting symptoms were pelvic fullness and lower abdominal pain in four patients, and one patient each with lower limb oedema, lower limb swelling leading to investigation and the diagnosis of a deep vein thrombosis, abdominal distension and constipation, and urinary frequency. These patients were evaluated further with abdominal and pelvic US (Fig. 1a) and CT (Fig. 1b). In the ninth patient US failed to detect a lymphocele or any other pathology, and the condition was presumed. This patient presented with abdominal distension and lower limb oedema. Imaging failed to show a lymphocele and the symptoms gradually resolved with no intervention or further investigation. In four patients there was spontaneous resolution of the symptoms and they were treated expectantly with regular US surveillance as outpatients until the resolution was complete. In these patients the main symptom was pelvic fullness. The remaining four patients with proven lymphoceles required percutaneous or fluoroscopically guided drainage, in the radiology suite by a uroradiologist with the patient under local anaesthesia. Each patient was given a course of prophylactic antibiotics during and for 72 h after the procedure.

Clinically significant lymphoceles were detected in eight of the nine symptomatic patients, using US or CT. One of the eight lymphoceles detected was a multilocular collection and none of them was infected. In
after laparoscopic pelvic lymph node dissection, but only a few became clinically evident and required treatment [4]. After pelvic node dissection the incidence of lymphoceles in one study was 54%, detected by CT, with lower rates after laparoscopic (8%) than after open pelvic lymph node dissection (27%). Despite an incidence of 27%, only three patients (2.3%) had clinically significant lymphoceles [5]. This shows that not only is the rate of lymphocele formation lower after laparoscopic surgery, but that the overall incidence of clinically significant lymphoceles was low. Additionally, retroperitoneal [6] and groin [7] lymphoceles may arise after inserting vascular grafts [8].

Percutaneous aspiration or drainage and microbiological testing of the fluid has been suggested before procedures such as internal drainage, to exclude a urinoma and superinfection in the management of renal transplant patients and lymphoceles [9]. Treatments include controlled percutaneous drainage [10], with or without sclerotherapy, percutaneous catheter drainage [11], laparoscopic surgery [12,13] or open surgical drainage [14].

The symptoms of such a collection depend on the site, size and the presence of infection. A visible or palpable pelvic mass may be present, resulting in abdominal/pelvic pain. Symptoms or signs may be a result of venous/ureteric compression resulting in unilateral leg oedema and leg pain, hydronephrosis with deterioration in renal function, and deep vein thrombosis [15]. Fever and chills should raise the suspicion of an infected collection. The risk of infection is higher in immunosuppressed patients after kidney and pancreatic transplantation, although the use of steroids in these patients minimizes the formation of adhesions and loculation.

Treatment options depend on factors such as size, position, infection risk, localizations and the recurrence of the collections. Pelvic lymphoceles after radical or transplant surgery can be treated by single or recurrent percutaneous aspiration of lymphatic fluid [16], percutaneous drainage [11], sclerotherapy or open surgical methods. Surgical drainage reportedly gives 50–70% success and >90% success was reported after peritoneal marsupialization [17]. Disadvantages of this last technique include the requirement for a general anaesthetic, longer hospitalization, and surgical trauma.

In cases of transplant surgery, when collections can occur laterally and either inferior or posterior to the graft, the percutaneous approach may not be possible. Techniques such as laparoscopic fenestration [18] or open surgical marsupialization with or without omentopexy [19,20] may be more effective. Laparoscopic marsupialization may be considered in the renal transplant patient with a symptomatic lymphocele and no infection [9]. Larger collections may require a draining catheter [21] but this technique may need to be repeated because of recurrence in 80–90% of patients, increasing the risk of bleeding and infection [9].

Numerous sclerosants have been used, e.g. tetracycline, doxycycline, bleomycin, ethanol, povidone iodine and sodium amidotrizoate. These sclerosing agents produce undesirable inflammatory reactions [22], unlike simple percutaneous catheter drainage. In one series of patients after renal transplant, the incidence of lymphoceles was 26%; percutaneous drainage had a recurrence rate of 33%, compared to the instillation of a sclerosing agent (ethanol) after percutaneous drainage, which had a recurrence rate of 25%. There may be a role for sclerotherapy in treating lymphoceles, especially in recurrent lymphoceles before surgery is to be contemplated [23].

The role of heparin in the formation of lymphoceles remains contentious. An early paper [24] suggested a high risk when low-dose heparin prophylaxis was given, but other reports have not supported this [25]. Lymphoceles are reportedly increased with the use of heparin in both RP [26] and renal transplantation [27].

The intraoperative application of fibrin glue does not reduce the rate of lymphoceles after lymphadenectomy in patients with gynaecological malignancies [28] or after renal transplantation [29]. The technique of omentoplasty and omentopexy after pelvic lymphadenectomy during surgery for gynaecological malignancies has had promising results in one study [30], with the authors concluding that this resulted in a lower incidence of lymphoedema, lymphoceles and lymphocysts associated with severe complications.

The advantage of percutaneous controlled aspiration of lymphoceles is that it may be
done under local anaesthesia in the radiology department, rather than the operating theatre. Complications such as bleeding, infection and accidental transection of a transplanted ureter [31,32] have been reported with laparoscopic and open surgical drainage. Percutaneous drainage by a skilled interventional radiologist is associated with minimal morbidity, with patients requiring a shorter hospital stay.

In conclusion, lymphocele formation after retroperitoneal RP should be considered when lower abdominal symptoms are reported. US and short term complications after US guided puncture of gynaecologic lesions: evaluation after 1000 consecutive cases. Radiology 1993; 189: 161–4


Fujikawa K, Kigawa J, Hasegawa K et al. Effect of simple omentoplasty and omentopexy in the prevention


Correspondence: Amir Kaisary, Royal Free Hospital, Pond Street, London NW3 2QG, UK.
e-mail: amir.kaisary@btinternet.com

Abbreviations: US, ultrasonography; RP, radical prostatectomy.
Testosterone recovery and changes in bone mineral density after stopping long-term luteinizing hormone-releasing hormone analogue therapy in osteoporotic patients with prostate cancer

ROBIN WESTON, ASAD HUSSAIN, EMMANUEL GEORGE and NIGEL J. PARR
Arrowe Park Hospital, Wirral NHS Trust, Liverpool, UK
Accepted for publication 1 November 2004

OBJECTIVE
To investigate the rate of testosterone recovery and changes in bone mineral density in patients found to be osteoporotic while receiving luteinizing hormone-releasing hormone (LHRH) analogues after changing to antiandrogen monotherapy in an attempt to reduce further demineralization.

PATIENTS AND METHODS
Fifteen patients receiving LHRH analogue therapy for ≥1 year were identified as osteoporotic by distal forearm dual X-ray densitometry. They were then converted to antiandrogen monotherapy, and prostate specific-antigen (PSA) and total testosterone monitored at 3-monthly intervals. The forearm densitometry was repeated at 1 year.

RESULTS
All patients had some testosterone recovery; the mean (range) duration to initial detectable testosterone was 12.8 (6–22) months. Six patients had a normal testosterone level after a mean of 17.5 (14–30) months. In the year after stopping LHRH analogue therapy the mean bone mineral density (t-score) decreased by 7.2%.

CONCLUSIONS
Osteoporotic patients, after stopping LHRH analogues, continue to have suppressed levels of testosterone which have a detrimental effect on bone mineral density. We therefore would not advocate conversion to antiandrogen monotherapy to improve bone density, and suggest alternative therapeutic intervention e.g. bisphosphonate therapy, for these patients.

KEYWORDS
prostate carcinoma, osteoporosis, testosterone, hormone therapy

INTRODUCTION
Depot LHRH analogues are currently the most popular method of hormone manipulation for patients with carcinoma of the prostate. They are effective in delaying the progression of the disease and hence patients are often on this treatment for many years [1]. However, LHRH analogues, because of their testosterone ablative effects, disturb bone metabolism, resulting in osteoporosis, a widely recognized complication of long-term testosterone ablation [2,3]. Osteoporosis is characterized by low bone mineral density (BMD) and is asymptomatic, only clinically manifesting itself when a low-trauma ‘osteoporotic fracture’ occurs. Several studies show that the incidence of osteoporotic fractures in patients receiving LHRH analogues is far higher than the incidence of pathological fractures [4,5]. An alternative method of hormone manipulation which maintains testosterone levels is antiandrogen therapy. This is increasingly popular as monotherapy in prostate cancer, as it offers comparable survival outcomes and potential quality-of-life benefits [6,7]. In the present study we investigated the time taken for testosterone levels to recover in osteoporotic patients established on long-term LHRH therapy, after changing to antiandrogen monotherapy, and assessed the changes in BMD.

PATIENTS AND METHODS
The study comprised 15 osteoporotic patients enrolled between November 2000 and July 2002. The mean (range) follow-up was 18 (12–30) months. The BMD of the subendosteal forearm was measured by dual-energy X-ray absorptiometry (DEXA) using a densitometer; the system used has a unique protocol for evaluating BMD at the ultrasound radius and ulna. The BMD result is expressed as the mean bone mineral density (t-score) as a BMD of ≤−2.5 SD (below) the mean for a healthy population group aged 20–40 years (t-score ≤−2.5), with or without pre-existing fragility fractures. Osteopenia is defined by a t-score of −1.0 to −2.4 and a normal BMD t-score as ≥−1.0.

Eight patients were found to be osteoporotic while already receiving LHRH analogues, and a further seven were osteopenic at the initial scan before treatment, and subsequently went on to develop osteoporosis while on LHRH analogues. Six patients developed osteoporosis within a year; their mean (±) t-score on initial DEXA scanning was −2.07 (0.15), decreasing to −2.72 (0.13) after a year, while one further patient progressed to osteoporosis after 2 years. All patients had received 3-monthly depot goserelin 10.8 mg for ≥1 year, replaced by bicalutamide 150 mg once daily as an alternative monotherapy after osteoporosis was diagnosed, the first dose being 3 months after the last depot injection. They also received calcium and vitamin D supplement (Ca²⁺ 12.6 mmol and cholecalciferol 400 units once daily). Total
testosterone and PSA levels were measured at baseline and at =3-month intervals thereafter. A further forearm DEXA scan was taken a year after stopping LHRH analogue therapy.

To determine the normal testosterone levels in patients with prostate cancer before hormonal treatment, 30 consecutive patients presenting to our unit had their testosterone levels measured and forearm densitometry assessed (control group). The laboratory reference range for a normal testosterone level is 9–40 nmol/L. The two-tailed Student’s t-test was used for statistical comparison, with a statistically significant result assumed at P≤0.05.

RESULTS

The mean (range) age of the 15 osteoporotic patients was 72 (55–86) years, the median Gleason grade at diagnosis 6 (2–10), median tumour stage T3 (T1–T4), mean PSA 57 (1.7–312) ng/mL and the mean duration on goserelin therapy 27 (12–96) months. At (1.7–312) ng/mL and the mean duration on monotherapy was 7.2% (0.11) during this period of hypogonadism, from −3 (0.73) to −3.2 (0.70) [P=0.02].

FIG. 1. Testosterone recovery after stopping LHRH analogue therapy in 15 men with osteoporosis. The black horizontal line is the normal level (>9 nmol/L).

DISCUSSION

The BMD is testosterone-dependent and both the administration of LHRH analogues [8,9] and orchidectomy [10] have been associated with severe osteoporosis. The exact mechanism by which testosterone maintains BMD is not fully understood, but local aromatization of testosterone to oestradiol is necessary for normal bone homeostasis [11]. There is also evidence that prostate cancer itself is a significant risk factor for osteoporosis, and hence fractures, by causing disturbances in bone turnover and mineralization even before androgen-deprivation therapy [12–14].

Bone densitometry scanning amongst men being treated with LHRH analogues for prostate cancer will inevitably identify patients who are already osteoporotic. As there is an increased rate of fragility fracture resulting in significant morbidity and mortality [15], some form of therapeutic intervention is therefore indicated. Currently no therapy has been convincingly confirmed to be effective in preventing osteoporotic fractures in men. However, as it is known that LHRH therapy is responsible for BMD loss by testosterone suppression, we investigated whether changing from goserelin to bicalutamide would be beneficial. Bicalutamide is a pure nonsteroidal antiandrogen which inhibits the action of dihydrotestosterone and testosterone at target sites, by competitively binding to the cytosolic androgen receptor [16]; however, because of its effect on the hypothalamic-pituitary axis it causes an increase in circulating testosterone and oestrogen levels. We therefore postulated that if testosterone levels could sufficiently recover after the change in hormone manipulation, we might confirm a positive effect on BMD.
There are no published studies examining testosterone recovery in osteoporotic patients after stopping LHRH analogues and subsequently starting antiandrogen therapy. The largest study [17] examining testosterone recovery after androgen ablation examined 267 patients, all of whom received radiotherapy, and most (67%) received stilboestrol and cyproterone, with only nine having >2 years of androgen ablation. The authors showed that over half the men had normal testosterone levels after a year, and 89% after 3 years. Nejat et al. [18] reported on 68 men after withdrawing androgen deprivation therapy, 60% of whom had received external beam radiotherapy. They found that the median time to testosterone recovery was 7 months, after a median duration of androgen deprivation of 9 months. In contrast to the present study, they reported a statistically significant delay in testosterone recovery in patients receiving >2 years of LHRH analogue compared with treatment for <2 years. Radiation scatter affecting the testes may be a confounding factor in both these studies. Hall et al. [19] investigated 14 patients after a mean duration of 38.6 months on LHRH analogues, with castrate levels of testosterone being reported for a median of 6 months; however, the follow-up was limited to a year and therefore normalization of testosterone was not assessed.

The present results show that patients who develop osteoporosis while being treated with LHRH analogues will continue to have hypogonadism for a mean of 17.5 months after conversion to an antiandrogen. The control group showed that some patients may have mild hypogonadism before initial hormone therapy, and therefore we would not expect all the study group to achieve normal testosterone levels. However, Amin et al. [20], using data from the Framingham study, indicated that low levels, as opposed to castrate levels, of testosterone did not correlate with a decrease in BMD, although oestradiol levels have a strong and positive association with BMD in men. This raises the point that normal levels of testosterone may not be necessary for maintaining BMD, as has been shown with physiological functions such as potency, but the availability of some testosterone for aromatization to oestradiol is essential for normal bone homeostasis.

In the year after stopping LHRH analogues the decrease in bone mineral density was consistent with the low or castrate testosterone levels. Therefore, with castrate levels of testosterone remaining for a mean of 12.8 months, the present study showed that discontinuing LHRH analogue therapy is not sufficient to protect osteoporotic patients from further demineralization.

Although becoming more popular, the use of antiandrogen monotherapy in advanced prostate cancer is still controversial. Tachyphylaxis did not appear to be a problem in the present study, with PSA levels remaining low despite testosterone recovery. The two patients who had had a persistent rise in PSA levels to >0.5 ng/mL have failed to show a PSA response despite being rendered pharmacologically castrate by reinstating LHRH analogues. We suggest that this probably reflects the natural history of the prostate cancer in these patients, as opposed to the effect of changing their hormone manipulation.

There is no doubt from increasing reports that LHRH analogues cause a decrease in BMD and therefore increase the risk of osteoporotic fracture. Men are twice as likely as women to die within a year of a hip fracture and are more likely to become dependent on nursing homes after such fractures [15]. Urologists should be more aware of the risk of osteoporosis amongst their patients with prostate cancer receiving hormone manipulation.

The present study highlights the continued testosterone suppression after stopping long-term LHRH analogues and the detrimental effect on BMD. Conversion to antiandrogen therapy seems to offer no significant short-term benefit to these patients, and we therefore suggest alternative therapeutic intervention, e.g. bisphophonate therapy; further studies are required to investigate this.

CONFLICT OF INTEREST

None declared.

REFERENCES

1 Sarosdy MF, Schellhammer PF, Soloway MS et al. Endocrine effects, efficacy and tolerability of a 10.8-mg depot formulation of goserelin acetate administered every 13 weeks to patients with advanced prostate cancer. BJU Int 1999; 83: 801–6
7 Iversen P, Tyrell CJ, Kaisary AV et al. Casodex 150mg monotherapy compared with castration in patients with previously untreated nonmetastatic prostate cancer. Results from two multicenter randomised trials at a median follow-up of 4 years. Urology 1998; 51: 389–96
14 Hussain SA, Weston R, Stephenson RN, George E, Parr NJ. Immediate DEXA scanning reveals a high incidence of osteoporosis in advanced prostate cancer prior to hormonal manipulation. BJU Int 2003; 92: 690–4

Correspondence: Robin Weston, Wirral NHS Trust, Urology, Liverpool, UK. e-mail: robin.weston1@btopenworld.com

Abbreviations: BMD, bone mineral density; DEXA, dual energy X-ray absorptiometry.
Sexual, psychological and dyadic qualities of the prostate cancer 'couple'

CYNTHIA T. SOLOWAY, MARK S. SOLOWAY, SANDY S. KIM and BRUCE R. KAVA

Department of Urology, University of Miami School of Medicine, Miami, Florida, USA

Accepted for publication 29 November 2004

OBJECTIVES

To examine the levels of sexual, psychological and dyadic functioning of the prostate cancer 'couple' (as studies have shown that spouses/partners play an integral role in the patient's adjustment to prostate cancer treatment), to encourage the creation of innovative psychosexual interventions to be used in the outpatient setting, and to offer insights into a novel area of prostate cancer research.

PATIENTS AND METHODS

In all, 103 men newly diagnosed with prostate cancer, and their partners, were assessed in an academic outpatient setting using instruments measuring sexual function, depressed mood, psychological distress and dyadic adjustment.

RESULTS

The partners' mean scores on sexual function questions were 55.75, significantly higher than those of the patients (51.7, P=0.018), showing that partners perceived their sexual performance at a better level. Partners' mean scores on the depression and distress measures were also significantly higher. On those items that monitored the accuracy of the patients' perceptions of their sexual function, partners rated the patients significantly lower in ability to gain erections (patient/partner means 2.67/4.52; P<0.001) and to perform sexually (patient/partner means 1.38/4.68; P<0.001) than they rated themselves.

CONCLUSIONS

Information from this study could be useful in constructing interventions that allow the physician and the prostate cancer 'couple' to reflect on issues of sexual function and psychological distress that might once have been considered taboo. The results characterize the disparities between patients with prostate cancer and their partners on self-reported questionnaires, and underscore how important it is to hear the voice of the 'couple'.

KEYWORDS

prostate cancer, sexual function, depression, psychological distress, marital quality

INTRODUCTION

Major challenges confront men with prostate cancer and their partners. Because most men with prostate cancer are asymptomatic, it is not surprising that couples are not prepared for the diagnosis of prostate cancer and the difficult treatment decisions they face.

Quality-of-life concerns and patient values are important in determining treatment choice [1]. Patients might choose a treatment with a lower long-term survival rate to increase the possibility of remaining sexually potent [2]. For the partner, survival is paramount [3]. Although most partners wish to be an active participant in the patient's treatment decisions, they are much less concerned about the patient's sexual morbidity [3,4]. This challenges a traditional notion that sexual intercourse is equally important to the patient and his partner.

Nonetheless, erectile dysfunction, the most common long-term side effect of prostate cancer treatment, significantly affects the marital relationship [4]. Changes in role during the treatment and recovery periods may lead to emotional distancing, making sexual interactions difficult as the patient and his partner attempt to protect each other's dignity [5]. Often, the only discussion between the patient and his partner related to sexual function comes when couples are presented with treatment options. If there is a loss of sexual function after treatment, communication related to sexual function is likely to stop [6].

Two pilot studies from Memorial-Sloan Kettering Cancer Center, examining psychological distress in men with prostate cancer and their partners, suggested that the partner plays an integral role in the patient's adjustment to treatment [7,8]. In the few other studies where both the patient and partner were considered, sexual activity before diagnosis, and social and psychological resources, were predictors of sexual adjustment and as antecedent conditions that affected the couple's coping skills [5,9]. Building on these findings, we hypothesized that prostate cancer is a couple's disease and, consequently, at different points during treatment it might be the 'couple' that should be counselled as the 'patient'.

This study was conducted to define 'the couple' with newly diagnosed prostate cancer. Variables thought to be important were the levels of sexual, psychological and dyadic functioning, and sociodemographic factors. By examining differences within individual couples we hoped to encourage the creation of innovative psychosexual interventions for the outpatient setting, as well as to offer insights into a novel area of prostate cancer research.

PATIENTS AND METHODS

Data from 103 newly diagnosed, untreated men with prostate cancer and their partners were analysed in a study approved by the
Institutional Review Board at the University of Miami. Homosexual men were excluded from the study because too few partnered homosexual men were seen in the urology outpatient clinic for effective analysis. Following methods of convenience sampling, consecutive untreated referrals (patients, married or in committed relationships, and their partners) were identified in the academic outpatient setting and familiarized with the variables of the study by the urologist. The patient and his partner, after reading and agreeing to the terms of the informed consent, independently completed the questionnaires in the outpatient office. Thirty-five couples declined to participate.

The following instruments were selected: the Brief Index of Sexual Function for Women (BISF-W) [10] and The Brief Sexual Function Questionnaire for Men (BSFQ) [11] measured sexual satisfaction, desire, and activity. An appendix to the BSFQ, questions validating the accuracy of the man's responses, was added to the BISF-W. Ad hoc questions from the Sexual Adjustment Questionnaire (SAQ), an instrument designed to assess sexual function in alcoholics and their spouses, were added to both inventories [12]. The Beck Depression Inventory (BDI) [13] examined attitudes and symptoms frequently shown by depressed patients. The Profile of Mood States (POMS) [14] assessed overall distress and six mood states (tension-anxiety, depression-dejection, anger-hostility, vigour-activity, fatigue-inertia, and confusion-bewilderment). Visual analogue scales of distress (VAS) [15] were two horizontal VAS with equally spaced unlabelled intervals (0–10) characterizing the level of distress at the diagnostic evaluation and before treatment. The Dyadic Adjustment Scale (DAS) [16] evaluated dyadic satisfaction, dyadic cohesion, dyadic consensus, and the expression of affection. The Sociodemographic Questionnaire (SQ) provided demographic and medical information.

Descriptive statistical analysis, Pearson product-moment correlation, one-way ANOVA, independent t-tests, paired samples t-tests and multiple linear regression analysis were used to assess the results.

**RESULTS**

The sociodemographic characteristics are shown in Table 1; 85% of the study participants were 45–70 years old, with the mean ages of the partners and patients being similar. Of the couples, 95% were married and 83% were in relationships of >10 years. The study population was highly educated; nearly 43% of the participants had completed at least a bachelor's degree. The participants were also ethnically diverse (Table 1) and more than half were employed.

Most of the men presented at diagnosis with what was thought to be organ-confined prostate cancer, most having a PSA level of ≤10 ng/mL and more than half with a Gleason score of ≤6; 85% of the patients had been diagnosed within the last 3 months. During the evaluation, half of the patients felt it was 'not likely' they would be given a diagnosis of prostate cancer; only 37% of their partners were that optimistic. Because the patients were relatively young it was not surprising that 54% had no comorbid conditions.

In Table 1, the mean ages of the partners and patients being similar. Of the couples, 95% were married and 83% were in relationships of >10 years. The study population was highly educated; nearly 43% of the participants had completed at least a bachelor's degree. The participants were also ethnically diverse (Table 1) and more than half were employed.

Most of the men presented at diagnosis with what was thought to be organ-confined prostate cancer, most having a PSA level of ≤10 ng/mL and more than half with a Gleason score of ≤6; 85% of the patients had been diagnosed within the last 3 months. During the evaluation, half of the patients felt it was 'not likely' they would be given a diagnosis of prostate cancer; only 37% of their partners were that optimistic. Because the patients were relatively young it was not surprising that 54% had no comorbid conditions.

In Table 1, the mean ages of the partners and patients being similar. Of the couples, 95% were married and 83% were in relationships of >10 years. The study population was highly educated; nearly 43% of the participants had completed at least a bachelor's degree. The participants were also ethnically diverse (Table 1) and more than half were employed.

Most of the men presented at diagnosis with what was thought to be organ-confined prostate cancer, most having a PSA level of ≤10 ng/mL and more than half with a Gleason score of ≤6; 85% of the patients had been diagnosed within the last 3 months. During the evaluation, half of the patients felt it was 'not likely' they would be given a diagnosis of prostate cancer; only 37% of their partners were that optimistic. Because the patients were relatively young it was not surprising that 54% had no comorbid conditions.
of the study sample for ethnicity \( (P = 0.095) \), educational level \( (P = 0.440) \), patient’s PSA at diagnosis \( (P = 0.124) \), and patient’s Gleason score at diagnosis \( (P = 0.306) \).

Student’s \( t \)-tests were used to confirm that there were no significant mean differences of key variables within the two largest ethnic sample populations (non-Hispanic whites and Hispanics). There were no significant mean differences for depression, sexual function and dyadic relationship, but there were \( (P = 0.039) \) for psychological distress (POMS score), with Hispanics showing a higher mean score.

**COUPLES AT DIAGNOSIS**

The data were initially analysed using independent \( t \)-tests to determine if there were any significant differences in the individual men (patient) and women (partner) populations. As the term ‘patient’ was redefined for this study to include the prostate cancer ‘couple’, paired-sample \( t \)-tests were then used on all the data, consistent with similar studies [8,17], to ascertain whether the patient and his partner scored significantly different from each other.

For sexual function (Table 2), compared with the mean scores of normal controls and of depressed and impotent men examined with the BSFQ, the men in the current study appeared to present at diagnosis with several sexual function issues [11]. In the areas of sexual satisfaction, interest in sexual activity and physiological competence, the men’s mean scores were similar to depressed and/or impotent populations rather than normal controls (Table 2). For example, 65% were dissatisfied with their sex life, 55% expressed decreased frequency of sexual drive and sexual thoughts and 60% reported erections that were insufficient for penetration.

When comparing scores from the BISF-W [18] administered to healthy women (mean age 40.4 years) with partners and with surgically menopausal women (mean age 47.1 years), the present women functioned similarly to the surgically menopausal group, especially in the areas of arousal, pleasure/ orgasm and relationship satisfaction (Table 2). In only two of the seven BISF-W subtests (frequency and receptivity/initiation of sexual activity) did the present women have equivalent mean scores to healthy women with partners.

On the SAQ, the paired \( t \)-test results indicated that the partners were significantly more positive about the communication and sexual components in their relationship than were the patients (patient/partner means 51.70/55.75, \( P = 0.002 \)). Although the BISF-W was modelled after the BSFQ, the actual questionnaires were not identical. Twenty questions from each measure were re-coded to allow for comparability. Paired-sample \( t \)-tests showed that the mean partner score was significantly higher than that of the patients (patient/partner means 40.57/49.61, \( P < 0.001 \)), showing that partners perceived their sexual performance at a better level. Results also established that the partner was significantly more satisfied in the relationship than the patient. The patient had significantly higher mean scores on the frequency of sexual thoughts (patient/partner means 2.96/1.96, \( P < 0.001 \)) and the level of pleasure felt from sexual experiences (patient/partner mean 3.88/1.85, \( P < 0.001 \)). On those items that monitored the accuracy of the patients’ perceptions of their sexual function, the partners rated the patients significantly lower in ability to gain erections, with patient/partner means 2.67/4.52 (higher number lower score; \( P < 0.001 \)) and to perform sexually, with patient/partner means of

### TABLE 2 Partner and patient sexual function means

<table>
<thead>
<tr>
<th>Questionnaire variables</th>
<th>Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Female dimensions (BISF-W) [18]</strong></td>
<td></td>
</tr>
<tr>
<td>D1: Thoughts and desires</td>
<td>Healthy with partners</td>
</tr>
<tr>
<td>5.31</td>
<td>2.5</td>
</tr>
<tr>
<td>D2: Arousal</td>
<td>6.21</td>
</tr>
<tr>
<td>D3: Frequency of sex activity</td>
<td>3.9</td>
</tr>
<tr>
<td>D4: Receptivity/initiation</td>
<td>8.85</td>
</tr>
<tr>
<td>D5: Pleasure/ orgasm</td>
<td>4.91</td>
</tr>
<tr>
<td>D6: Relationship satisfaction</td>
<td>8.9</td>
</tr>
<tr>
<td>D7: Problems affecting sex function*</td>
<td>4.47</td>
</tr>
<tr>
<td>Composite score</td>
<td>(D1 + D2 + D3 + D4 + D5 + D6-D7)</td>
</tr>
<tr>
<td><strong>Male dimensions (BSFQ) [11]</strong></td>
<td></td>
</tr>
<tr>
<td>Sexual activity/performance</td>
<td>Controls</td>
</tr>
<tr>
<td>36.8</td>
<td>17.2</td>
</tr>
<tr>
<td>Satisfaction</td>
<td>13.7</td>
</tr>
<tr>
<td>Interest</td>
<td>9.2</td>
</tr>
<tr>
<td>Physiological competence†</td>
<td>3.3</td>
</tr>
<tr>
<td>‘Paired’ sexual function scores</td>
<td>Patient mean</td>
</tr>
<tr>
<td>Total SAQ</td>
<td>51.70</td>
</tr>
<tr>
<td>Total BSFQ and BISF-W</td>
<td>40.57</td>
</tr>
</tbody>
</table>

*Lower mean score suggests fewer problems affecting sexual function. In all other variables higher mean score suggests higher functioning. †Lower mean score suggests higher physiological competence.
The mean POMS total mood disturbance score of the partner was also significantly higher than the patient’s. Of the six mood states measured, the means, all within the normal range, of the tension-anxiety, depression-dejection, anger-hostility, fatigue-inertia and confusion-bewilderment subscales were significantly greater in the partner than in the patient. These findings were similar to the scores computed for men and women independently. The VAS results confirmed that partners were significantly more distressed at evaluation and diagnosis than the patients. There were no significant differences in the means of the patient/partner responses on the DAS or its four subtests.

To assess the strength of the instruments in measuring study variables, multiple regression analysis was conducted to evaluate if the total BDI, POMS and DAS score (and/or their subtest scores), as well as any sociodemographic variable, predicted sexual function. The analysis showed that the predictors of sexual activity were dyadic cohesion (DAS subtest), ethnicity, employment status and the patient's thoughts about his chance of being diagnosed with cancer. The linear combination of these factors in the patients and partners was significantly related to sexual activity ($P < 0.001$). The sample correlation coefficient was 0.542, indicating that ~30% of the variance of sexual function could be accounted for by these factors.

Correlations assessed between depression-dejection (POMS subtest) and the BDI, and between comparable BISF-W/BSFQ items and the SAQ questions, as well as the results from the multiple linear regression analysis, were helpful in validating that the instruments chosen for the study created an integrated and focused tool.

**DISCUSSION**

Since the mid-1990s there has been extensive research into health-related quality of life (HRQoL) aspects of prostate cancer, concentrating on the patient's level of functioning and emotional status [5,19]. No HRQoL studies have examined sexual function, depression, psychological distress and dyadic relationship levels in the patient and his partner. The present study provides evidence that the prostate cancer ‘couple’ at diagnosis has complex and disparate needs, and shows a need for psychosexual interventions that augment current treatments for sexual and psychological problems arising from a prostate cancer diagnosis.

**THE ROLE FOR THE PARTNER**

Researchers have discovered that partners are often the communication conduit between the patient and his physician, in addition to serving as key advocates during diagnosis and treatment [9]. However, studies have reported that the partner often feels ignored by the patient’s physician [9]. Sneeuw et al. [17] advocated that spouses serve as proxy ‘raters’ when assessing HRQoL of the patient. Therefore, the physician might wish to include the partner in the consultation process, with informational and emotional support offered to both [17,20]. There might also be poor agreement between the professional and patient assessment of distress, with physicians underestimating severity [20]. Using questionnaires before treatment, as in the present study, seems to be informative to the physician and therapeutic for couples, as it stimulates discussion about sexual and emotional issues relevant to the couple’s concerns [20].

**THE IMPACT OF THE PARTNER'S PSYCHOLOGICAL DISTRESS ON OUTCOME**

In the 1994 Memorial-Sloan Kettering Cancer Center study, researchers examined the effect of disease stage and treatment regimen on HRQoL in patients with prostate cancer and in their partners [8]. The authors concluded, as in the present study, that partners had...
significantly higher levels of psychological distress, and needed to be assessed regularly to identify how that distress might affect the patient’s adaptation to his prostate cancer. Patient and partner depression were measured in a later study [7], and 31% of evaluable patients and their partners were referred for psychological assessment. The present study confirmed that, at diagnosis, 30% of both patients and partners might be appropriate for referral for further evaluation and treatment, and that partners of patients with prostate cancer have significantly higher depression scores than the patients. The question remains as to whether patients and partners are being evaluated and/or referred by their physician for their depression, a diagnosis that might ultimately affect adjustment to treatment, and the outcome.

The POMS total mood disturbance score and the subtests of depression-dejection, tension-anxiety, fatigue-inertia, confusion/bewilderment and anger/hostility were also significant, suggesting that the partners are more psychologically distressed and, in fact, might be distracted (higher confusion/bewilderment score) by their distressed mood. In addition, the Hispanic patient and his partner were significantly more distressed than the white non-Hispanic couples. Together with the fact that the partner’s mean score on each VAS was significantly higher than the patient’s, we concluded that partners are more likely to be psychologically distressed than patients, and this should be carefully considered, as the partner’s psychological distress might predict a greater HRQoL problem index for men with prostate cancer [1].

WHAT ARE THE REAL SEXUAL FUNCTION ISSUES?

The return of sexual function after treatment for prostate cancer depends on patient age, the clinical and pathological stage of his disease, the treatment method and, in the surgical patient, whether the neurovascular bundles have been preserved [21]. In the present study, 69 of 103 patients elected to have radical surgery; 46 (66%) of those patients reported normal erectile function to the urologist at diagnosis. Interestingly, in the same study population, 75 men (78%) admitted having erections that were not sufficient for penetration, when questioned more specifically. At best, 66% of all patients, irrespective of age, are potent after radical surgery [21,22]. Patients undergoing external beam radiation therapy might, because of age and stage of disease, have poorer sexual function outcomes [4]. Therefore up to half of all patients treated for prostate cancer might have erectile dysfunction 12 months after treatment. Moreover, partners reported that patients had lower levels of sexual performance and poorer quality erections than study patients themselves reported. Thus, if partners were asked to assess the patient’s erectile function after treatment, it might be even less than half of all patients treated that have erections adequate for sexual activity. The partner’s decreased level of sexual function must also be included in the equation. Given the emphasis that many patients place on sexual function, physicians might find it helpful to address the challenging problems facing 50% of men with erectile dysfunction that might not be resolved by current medical therapies.

While technological assistance for erectile dysfunction (e.g. injections, prostheses) might help some patients adjust to what they believe is a loss of virility, partners might find these methods unappealing [23]. To confound matters, aids to promote erections might make patients feel vulnerable and awkward and, ultimately, produce barriers to seeking any kind of help for sexual problems [4]. It has been reported that physicians avoid discussions on the impact of sexual problems because of lack of knowledge or comfort with issues of sexual intimacy [1,9,23]. This leaves couples to ‘grieve’ in silence over the loss of an integral part of their marriage [1,9]. Thus, some investigators, including the present authors, suggest that counselling should be expanded from primarily helping patients to choose an appropriate prostate cancer treatment, to facilitating the couples’ successful adjustment to treatment outcomes [1].

Partners are extremely reticent about addressing sexual issues for fear of further increasing patient anxiety about the diagnosis of prostate cancer [5]. Tacitly they wish for patients to have erections, understanding that erections are how men define their masculinity [6]. Patients, on the other hand, are demoralised by their changing role and the potential for impaired performance, and have reported that they assume, based on their partner’s silence, that the loss of sexual relations has little effect on the partner [1,9]. Left to adjust to the loss of their sexual relationship in silence, both the patient and partner often feel isolated [9]. For couples, this isolation can lead to distress, and distress might place patients with prostate cancer at risk of poor adjustment to their disease. Recognizing from the present study that the partners are already distressed over the diagnosis and the treatment choices, the additional distress caused by sexual isolation could be even more detrimental to patient outcome. As perhaps only half of all patients who report they are potent at diagnosis will have an acceptable level of potency after treatment, it is critical to develop new psychosexual educational interventions as alternatives for pharmacological or technological options. Even before any decision is made about treatment, discussion of these issues could help to address differences about issues of sexual activity, psychological distress and intimacy and, ultimately, enhance sexual satisfaction after treatment.

Most of the couples studied were in long-term relationships. Moreover, the scores on the DAS describe a sample of couples that showed dyadic cohesion, consensus, affection and satisfaction. In a study examining sexuality and marital life, Trudel [24] concluded that there was a statistically significant relationship between marital functioning and sexual behaviour. As dyadic cohesion was a predictor of sexual function in the present study, there is obvious potential for prostate cancer ‘couples’ to adapt to the sexual function outcomes of treatment. That adjustment is possible if couples continue to communicate during the diagnosis, treatment and the recovery process on critical sexual issues, and if partners can be encouraged to be active in the decision-making process regarding treatment and its sexual consequences.

Because of the nature of the present population, the study design had at least one limitation. A convenience-sampling model was used to recruit patients seeking treatment at an academic outpatient clinic, but the sample might not be representative of the entire population of patients with prostate cancer and their partners. Nevertheless, the information from this study could be very useful in constructing a receptive environment (i.e. sexual, psychological and dyadic assessment; psychosexual educational interventions) where the newly diagnosed patient with
prostate cancer and his partner can, with their physician, begin to reflect on the WHO definition of sexual health, the ‘integration of somatic, emotional, intellectual and social aspects’ of being sexual [3], in ways that might once have been considered taboo.

ACKNOWLEDGEMENTS

This study was supported by the Spector Family Foundation donation awarded to Mark S. Soloway, MD, to use at his discretion to fund prostate cancer research.

CONFLICT OF INTEREST

None declared. Source of funding: private donation from Spector Family Foundation.

REFERENCES

12 O’Farrell TJ, Kleinke CL, Cutter HS. A Sexual Adjustment Questionnaire to use in therapy and research with alcoholics and their spouses. J Subst Abuse Treat 1997; 14: 259–68
20 Cliff AM, MacDonagh RF. Psychosocial morbidity in prostate cancer: II. A comparison of patients and partners. BJU Int 2000; 86: 834–9

Correspondence: Mark S. Soloway, PO Box 016960 (M-814), Miami, Florida 33101, USA. e-mail: msoloway@miami.edu

Abbreviations: BISF-W, The Brief Index of Sexual Functioning for Women; BSFQ, The Brief Sexual Function Questionnaire for Men; SAQ, The Sexual Adjustment Questionnaire; BDI, The Beck Depression Inventory; POMS, Profile of Mood States; VAS, Visual Analogue Scales of Distress; DAS, The Dyadic Adjustment Scale; SQ, The Sociodemographic Questionnaire; HRQoL, health-related quality of life.
Correlation between clinical and pathological staging in a series of radical cystectomies for bladder carcinoma

VINCENZO FICARRA, ORIETTA DALPIAZ, NAJATI ALRABI, GIACOMO NOVARA, ANTONIO GALFANO and WALTER ARTIBANI
Department of Urology, University of Verona, Italy

Accepted for publication 29 October 2004

OBJECTIVE

To analyse the rate of concordance between the clinical and pathological Tumour-Nodes-Metastasis staging systems in a homogeneous series of patients who had undergone radical cystectomy for locally advanced or recurrent multifocal superficial bladder carcinoma.

PATIENTS AND METHODS

The clinical data of 156 patients who had undergone radical cystectomy and bilateral iliaco-obturator lymphadenectomy for bladder cancer in our department were analysed retrospectively.

RESULTS

The clinical stage of the primary tumour was carcinoma in situ in three patients (1.9%), cT1 in 67 (42.9%), cT2 in 70 (44.9%), cT3 in five (3.2%) and cT4 in nine (5.8%). Clinical lymph node involvement was detected in 19 patients (12.2%). The differences between clinical and pathological stages were statistically significant ($P < 0.001$), the concordance was moderate ($k = 0.27$, $P < 0.001$). Of the 70 patients with cT1, 40 (57%) were reconfirmed as having pathological stage ≤T1; of the 70 with cT2, 16 (23%) had pT2 carcinoma. Of the 140 patients with clinically organ-confined (≤T2) neoplasms, 70 (50%) had been understaged after radical cystectomy. The clinical and pathological systems were statistically overlapping for locally advanced cases only. Pathological lymph node involvement was diagnosed in 45 patients (28.8%); this was foreseen with pelvic computed tomography in 19 (12%) only ($P < 0.001$). All patients designated cN+ were also pN+.

CONCLUSION

These data confirm the high risk of clinical understaging of both local extension of the primary tumour and lymph node involvement.

KEYWORDS

bladder cancer, TCC, squamous cell carcinoma, survival, radical cystectomy, staging, TNM

INTRODUCTION

The definition of the local extension of the primary tumour and the eventual detection of loco-regional lymph node or distant metastases are fundamental steps both in treatment planning and assessing the outcome for patients with cancer. The need to compare overall and cancer-specific survival data, both in terms of stratifying patient risk and treatment efficacy, makes mandatory the use of a worldwide staging system [1]. The TNM staging system is the most widely used to report local, lymph node and distant extension of neoplasms. The latest edition of the TNM system for bladder cancer was defined by Union International Contre le Cancer and American Joint Committee on Cancer in 2002 [2].

As far as local extension of the primary tumour is concerned, bladder cancer staging is based on histological analysis of the transurethral resection (TUR) specimen, bimanual examination under general anaesthesia before and after TUR, and on imaging (ultrasonography, CT and MRI). Moreover, the same imaging aims to detect clinical loco-regional lymph node involvement and distant metastasis, as do chest X-rays or bone scans.

Despite the relevant clinical role of staging in selecting the most appropriate therapy for patients with bladder cancer, reports highlight that 30–50% of patients undergoing radical cystectomy had been understaged, both for local extension of the primary tumour and lymph node involvement [3–5]. The most relevant clinical issues are a more appropriate staging of cT1 cancers and the preoperative identification of those patients with locally advanced and/or loco-regional lymph node-involving tumours (cT3-4 and/or cN+). The accuracy of clinical staging of cT1 tumours can be markedly improved if bladder wall smooth muscle is present in the initial TUR specimen. A second staging TUR is strongly recommended in all cases with no smooth muscle in the specimens [4]. However, the presence of residual cancer at the second TUR and the pathological findings of radical cystectomy specimens underscore the inaccuracy of clinical staging in patients with cT1. Bimanual examination under general anaesthesia and CT have a low sensitivity for defining the local extension of tumours. Bimanual palpation is subjective and depends on both the experience of the surgeon and the physical constitution of the patient. CT can misdiagnose 30–50% of locally advanced bladder cancers [6–10]. Moreover, the currently available imaging techniques cannot identify loco-regional lymph node micrometastases.

Thus the purpose of the present study was to analyse the rate of concordance between clinical and pathological staging systems in a homogeneous series of patients who had undergone radical cystectomy for locally advanced or recurrent multifocal superficial bladder carcinoma.

PATIENTS AND METHODS

We retrospectively analysed the clinical data of 156 patients who had undergone radical
cystectomy and bilateral iliaco-obturator lymphadenectomy for bladder cancer in the Department of Urology, University of Verona between 1995 and 2001. The indication for radical cystectomy included tumour invasion of the muscularis propria (≥T2) or high-grade, invasive bladder tumours associated with carcinoma-in-situ (CIS), CIS refractory to intravesical immunotherapy, or recurrent multifocal superficial disease refractory to repeat TUR with or without intravesical therapy.

Clinical staging was always associated with TUR, bimanual examination before and after TUR under general anaesthesia, chest X-ray and abdominal and pelvic CT. The presence of concomitant upper urinary tract neoplasms was assessed by IVU or CT. Bone scan and brain CT were used when indicated by signs and symptoms. Radical cystectomy was not offered to patients with metastatic bladder cancer.

All patients had a standard surgical procedure, including meticulous pelvic-iliac lymphadenectomy with en bloc radical cystectomy, as described by Skinner and Lieskovsky [11]. All cystectomy specimens were examined using the same pathological protocol. Several sections were obtained from the tumour, the bladder wall and mucosa adjacent to and distant from the tumour, along with the ureters and regional lymph nodes. In men, tissue was obtained from the seminal vesicles and prostate, and in women from ovaries, uterus and vagina when appropriate [12].

Clinical and pathological stages were reported according to the 2002 TNM system [2], but combining CIS and T1 (cT1), T2a with T2b (T2), T3a with T3b (T3) and T4a with T4b (T4). The WHO 1998 classification was used to assign a histological tumour grade [13].

The Pearson chi-square test was used to compare categorical variables. The χ² statistic, a measure of agreement between observers that corrects for chance agreement, was used to evaluate the concordance between the clinical and pathological stages. The grade of concordance has been defined as ‘fair’, for a χ² of 0–0.2, moderate for 0.21–0.45, substantial for 0.46–0.75 and almost perfect for 0.76–0.99 [14]. In all the statistical analyses, a two-sided P < 0.05 was considered to indicate statistical significance. All the clinical and pathological data were collected in a database and analysed using commercial software.

RESULTS

Table 1 summarizes the clinical and pathological characteristics of the 156 patients analysed; in 94 (60%) radical cystectomy was indicated after the progression of an initially superficial bladder carcinoma, previously treated with TUR and intravesical chemo- or immunotherapy. In these cases the mean (SD, range) time elapsed between the initial diagnosis of bladder cancer and cystectomy was 59.96 (5.1, 3–264) months. In the other 62 patients (40%), bladder neoplasms were muscle-invasive at the time of initial diagnosis. The pathological analysis of the radical cystectomy specimen identified bladder TCC in 86% and squamous cell carcinoma in 14%. The pathological stage of the primary tumour is also shown in Table 1.

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>Mean (SD) [range] or n (%)</th>
<th>TABLE 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>65.6 (9.01) [36–91]</td>
<td>The main clinical and pathological characteristics of the 156 patients</td>
</tr>
<tr>
<td>Male/female, %</td>
<td>90.4/9.6</td>
<td></td>
</tr>
<tr>
<td>Bladder cancer history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>first diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>progression of superficial cancer</td>
<td>94 (60.3)</td>
<td></td>
</tr>
<tr>
<td>Upper urinary tract neoplasm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>absent</td>
<td>147 (94.2)</td>
<td></td>
</tr>
<tr>
<td>present</td>
<td>9 (5.8)</td>
<td></td>
</tr>
<tr>
<td>Upper urinary tract obstruction</td>
<td>107 (68.6)</td>
<td></td>
</tr>
<tr>
<td>absent</td>
<td>37 (23.7)</td>
<td></td>
</tr>
<tr>
<td>unilateral</td>
<td>12 (7.7)</td>
<td></td>
</tr>
<tr>
<td>bilateral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>primary tumour</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CIS/T1</td>
<td>70 (44.9)</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>70 (44.9)</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>7 (4.5)</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>9 (5.8)</td>
<td></td>
</tr>
<tr>
<td>Lymph node</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cN0</td>
<td>137 (87.8)</td>
<td></td>
</tr>
<tr>
<td>cN+</td>
<td>19 (12.2)</td>
<td></td>
</tr>
<tr>
<td>Histological tumour grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>G2</td>
<td>10 (6.4)</td>
<td></td>
</tr>
<tr>
<td>G3</td>
<td>146 (93.6)</td>
<td></td>
</tr>
<tr>
<td>Pathological characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histological type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TCC</td>
<td>134 (85.9)</td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>22 (14.1)</td>
<td></td>
</tr>
<tr>
<td>Pathological stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>primary tumour</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ pT1</td>
<td>42 (26.9)</td>
<td></td>
</tr>
<tr>
<td>pT2</td>
<td>28 (17.9)</td>
<td></td>
</tr>
<tr>
<td>pT3</td>
<td>59 (37.8)</td>
<td></td>
</tr>
<tr>
<td>pT4</td>
<td>27 (17.3)</td>
<td></td>
</tr>
<tr>
<td>Lymph node</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pN0</td>
<td>111 (68.6)</td>
<td></td>
</tr>
<tr>
<td>pN+</td>
<td>45 (31.4)</td>
<td></td>
</tr>
</tbody>
</table>
Table 2 shows the correlations between clinical and pathological stages of the primary tumour. The concordance between clinical and pathological staging systems was moderate (P < 0.001). Only 40 of the 70 patients with ≤cT1 (57%) were reconfirmed as having ≤pT1 bladder cancer. In this subgroup the percentage of upstaging correlated with the bladder cancer history; in particular there was upstaging in two-thirds of those with a first diagnosis of cT1 and in 30% of those where the diagnosis of cT1 was a progression after a previous diagnosis of cT1 bladder cancer. In one TUR only. To date, to the best of our knowledge, our study is the largest to date involving a comparison of clinical and pathological staging of the primary tumour for all tumours and tumours for TCC.

Only 16 of the 70 patients who had cT2 (23%) had pT2 stage carcinoma; among the 140 patients with neutrophilic (≤cT2) neoplasms, 70 (50%) were understaged after radical cystectomy. The clinical and pathological staging systems overlapped statistically only for locally advanced bladder cancer. Table 2 also shows the correlations between clinical and pathological stages of the primary tumour in patients with TCC only. In this subgroup there was moderate concordance between clinical and pathological stages (P < 0.001).

Pathological lymph node involvement was diagnosed in 45 patients (29%), foreseen on pelvic CT in only 19 (12%) (k = 0.51, P < 0.001). All patients with clinical lymph node involvement were also pN+

**DISCUSSION**

This study confirmed the moderate correlation between the clinical and pathological TNM staging system in bladder cancer. The exact definition of clinical T1 bladder cancers is relevant for the therapeutic strategy. T1 tumours could be adequately treated conservatively with TUR and intravesical immunotherapy. This strategy is inappropriate if the tumours are understaged, for which the standard treatment could currently be radical cystectomy and/or systemic chemotherapy.

In our experience, 43% of patients staged cT1 bladder cancers were upstaged at pathological examination of the radical cystectomy specimen. The results were even worse for patients with cT2 disease, who were correctly staged in only 23%. On the contrary, there was a substantial correlation in cT3–4 tumours.

The present results were similar to those reported previously (Table 3) [15–23]. Paulson et al. [16] found an understaging rate of 35% in a cohort of patients treated with radical cystectomy for cT1 stage cancers. Freeman et al. [19], analysing data from 182 patients for clinical stage ≤cT1 bladder cancer, reported understaging rates of 19%, 40% and 34% in stage cTa, cT1 and ≤cT1, respectively. In two recent series [21,23] the authors underlined that TUR understaged the primary tumour in 52% and 46% of cases, respectively. More reports support the need to repeat a second staging TUR at 2–6 weeks after the first [3]. The possible indications for a repeat TUR could be clinical T1 tumours, any G3 lesions, all samples with no smooth muscle in the surgical specimen, and all those in which cancer tissue was detected in the TUR specimen obtained from the margins separately after macroscopically complete resection [24]. Herr [4], in a series of 150 patients, reported that 19.8% of ≤cT1 stage cancers were upstaged to cT2 after repeat TUR. Moreover, stratifying by clinical stage, 32% of cTa-Tis and 27.6% of T1 cases were understaged at the second TUR. The overall understaging rates were 14% and 49% in the cases with and with no smooth muscle in the initial TUR specimen, respectively. Generally, a second TUR could modify the therapeutic strategy in a proportion of patients, i.e. 24–33% [3,4]. Similarly, Schips et al. [24] detected residual cancer on repeat TUR in 40 of 110 (36%) patients analysed, and Grimm et al. [5] reported higher 3- and 5-year recurrence-free survival rates in patients who had had a second TUR than in those who had undergone TUR only. To date, to the best of our knowledge, our study is the largest to date involving a comparison of clinical and pathological staging of the primary tumour for all tumours and tumours for TCC.

**TABLE 2** The correlation between clinical and pathological staging of the primary tumour for all tumours and for TCC

<table>
<thead>
<tr>
<th>Stage</th>
<th>&lt;pT1</th>
<th>pT2</th>
<th>pT3</th>
<th>pT4</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>All, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤cT1</td>
<td>40 (57)</td>
<td>11 (16)</td>
<td>13 (19)</td>
<td>6 (9)</td>
<td>70 (100)</td>
</tr>
<tr>
<td>cT2</td>
<td>2 (3)</td>
<td>16 (23)</td>
<td>42 (60)</td>
<td>10 (14)</td>
<td>70 (100)</td>
</tr>
<tr>
<td>cT3</td>
<td>1</td>
<td>4</td>
<td>2</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>cT4</td>
<td></td>
<td>9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>42 (27)</td>
<td>28 (18)</td>
<td>59 (38)</td>
<td>27 (17)</td>
<td>156 (100)</td>
</tr>
<tr>
<td>TCC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤cT1</td>
<td>40 (61)</td>
<td>11 (17)</td>
<td>10 (15)</td>
<td>5 (8)</td>
<td>66 (100)</td>
</tr>
<tr>
<td>cT2</td>
<td>2 (4)</td>
<td>15 (27)</td>
<td>30 (55)</td>
<td>8 (15)</td>
<td>55 (100)</td>
</tr>
<tr>
<td>cT3</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>cT4</td>
<td></td>
<td>7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>42 (31)</td>
<td>27 (20)</td>
<td>43 (32)</td>
<td>22 (16)</td>
<td>134 (100)</td>
</tr>
</tbody>
</table>

**TABLE 3** The clinical understaging rate of the primary tumour in the most relevant series of radical cystectomy

<table>
<thead>
<tr>
<th>Study</th>
<th>N patients</th>
<th>Clinical stage</th>
<th>Understaging rate, %</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>[15]</td>
<td>261</td>
<td>all</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>[16]</td>
<td>na</td>
<td>CT1</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>[17]</td>
<td>130</td>
<td>all</td>
<td>41.5</td>
<td></td>
</tr>
<tr>
<td>[18]</td>
<td>220</td>
<td>≤cT1</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>[19]</td>
<td>182</td>
<td>≤cT1</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ta</td>
<td>19</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>T1</td>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>[20]</td>
<td>1026</td>
<td>all</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>[21]</td>
<td>105</td>
<td>all</td>
<td>52.3</td>
<td></td>
</tr>
<tr>
<td>[22]</td>
<td>78</td>
<td>≤cT1</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>[23]</td>
<td>169</td>
<td>all</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>156</td>
<td>≤cT1</td>
<td>42.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>cT2</td>
<td>74.3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

na, not available.
knowledge, the only available data comparing pathological stage and clinical stage after a second TUR were reported by Dalbagni et al. [25]; they analysed 15 patients with clinical stage T1 bladder carcinoma after a second TUR and who had had immediate radical cystectomy. Only two of 15 patients had pathological stage ≥ T2. However, other authors indicate the morbidity and costs related to readmission and second anaesthesia [28], while others denied the usefulness of such a procedure unless smooth muscle was absent in the initial TUR specimen [27]. A second TUR was not routinely used in the present patients, not being part of the current clinical practice at our department during the years analysed for this report.

Imaging techniques provide insufficient information to the clinical staging, mostly limited to assessing loco-regional lymph node involvement. Paik et al. [8], analysing 82 patients who had abdominal and pelvic CT, reported an overall accuracy of up to 55%, with understaging and overstaging rates of 39% and 6%, respectively. Similar data were reported by Kim et al. [10] in 36 patients. The detection of lymph node involvement was an important limitation of CT. In our experience, CT identified only a third of patients with pathological lymph-node involvement. The present data and the analysis of earlier reports underlines the need for more reliable staging techniques. Promising but insufficient data are currently available for the use of MRI in the clinical staging of bladder cancer. Tavares et al. [28] and Jager et al. [29] reported higher sensitivity rates in staging local extension of the primary tumour in two small cohorts of patients with locally advanced bladder cancer, while the overall accuracy in lymph node assessment was disappointing, with false-negative rates as high as 40%. The results of other imaging techniques, e.g. positron emission tomography, are still preliminary [30] and not very encouraging.

CONFLICT OF INTEREST

None declared.

REFERENCES

2 Sobin DH, Witteking CH eds. TNM Classification of Malignant Tumours, 6th edn. New York: Wiley-Liss, 2002
23 Chang BS, Kim HL, Yang XJ, Steinberg GD. Correlation between biopsy and radical cystectomy in assessing grade and depth of invasion in bladder urothelial carcinoma. Urology 2001; 57: 1063–6
30 Hain SF, Maisey MN. Positron emission tomography for urological tumours. BJU Int 2003; 92: 159–64

Correspondence: Vincenzo Ficarra, Department of Urology, University of Verona, Piazzale Ludovico Scuro, 37100 – Verona, Italy. e-mail: vincenzo.ficarra@univr.it

Abbreviations: TUR, transurethral resection; CIS, carcinoma in situ.
A comparison of the pathology of transitional cell carcinoma of the bladder and upper urinary tract

GRANT D. STEWART, SIMON V. BARIOL, KEN M. GRIGOR*, DAVID A. TOLLEY and S. ALAN McNEILL
Departments of Urology and *Pathology, Western General Hospital, Edinburgh, UK.

Accepted for publication 8 December 2004

OBJECTIVE

To clarify the histopathological patterns of upper and lower urinary tract transitional cell carcinomas (TCCs), as previous reports suggest that upper urinary tract TCCs have a greater tendency towards high-grade disease than bladder TCCs, of which most are low-grade and low-stage tumours.

PATIENTS AND METHODS

All patients presenting with TCC of bladder or upper urinary tract between February 1991 and December 2001 at one institution were identified. Further patient information was obtained from the hospital database and case-note review.

RESULTS

In all, 164 patients with upper urinary tract TCC and 2197 with bladder TCC were identified. There was a correlation between grade and stage of both upper urinary tract and bladder TCCs. 35% of the upper tract TCCs were classified as grade 2 and 44% as grade 3, while for bladder TCCs, 31% of lesions were classified as grade 2 and 35% as grade 3 ($P = 0.003$). Of the upper urinary tract lesions 33% were stage pT2–T4, compared with only 20% of bladder TCCs ($P = 0.001$).

CONCLUSIONS

Upper urinary tract TCC is a higher grade and stage disease than bladder cancer, a finding that emphasizes the need for aggressive treatment of upper urinary tract TCC. If endourological management of upper urinary tract TCC is considered, histopathological determination of tumour grade before treatment is essential.

KEYWORDS
carcinoma, transitional cell, bladder, kidney, ureter, TCC

INTRODUCTION

It has been previously stated that most TCCs are low-grade (G1 and G2) and low-stage tumours (pT1a and pT1), even when the upper tract is affected [1], but several published studies have shown a varying distribution of grade and stage of upper urinary tract TCC. Most studies have shown a preponderance of high-grade (G3) and stage (pT2–4) disease when the upper urinary tract is affected [2–6]. Mazeman [2], in a review of 893 patients with upper urinary tract TCC, found that 55.3% of tumours were high-grade. Hail et al. [4], in a cohort of 252 patients with upper urinary tract TCC, found that 42.5% had high-grade disease and 43.8% had high-stage tumours. By contrast, Anderström et al. [7] found that 75% of patients with upper urinary tract TCC had low-stage and -grade tumours.

There is an established correlation between the grade and stage for TCC affecting the upper and lower urinary tract [6,8–12]. Furthermore, advanced grade and stage is associated with a poorer prognosis, which influences management decisions [1]. Keeley et al. [13] showed that accurate grading and staging is possible from specimens obtained by ureteroscopic biopsy of upper urinary tract TCC, as information obtained from these biopsies correlated well with that of the final pathological specimen.

Although endourological management is indicated for patients with a single kidney, synchronous bilateral disease, chronic renal failure or those unfit for major surgery [14], there is a trend towards endourological management of patients with a normal contralateral kidney. However, this recommendation is confined to the management of small, low-grade lesions [14–16].

We sought to evaluate the stage and grade of upper and lower urinary tract TCC using a large series over a 10-year period, to assess differences in the pathology of the disease affecting the different parts of the urinary tract.

PATIENTS AND METHODS

All patients with TCC of the bladder or upper urinary tract presenting to the Department of Urology at the authors’ institution between February 1991 and December 2001 were identified from a prospectively collected pathology database. Histological material was reviewed by one uropathologist (K.M.G.); data from patients’ initial pathology were included in the analysis. Most of the bladder TCCs in this study were resected endoscopically, and we are confident that these patients have not been understaged because of inadequate muscle in the specimen. The experienced pathologist who reviewed all the specimens gave a staging of pTx if there was any doubt of the stage from the specimen. Further data were obtained from the hospital database and patient notes, which included patient demographics, anatomical location of the tumour and method of resection. Data on disease recurrence, disease-specific survival and overall survival were not collected, as it was not the aim of the study to evaluate these factors. Independent statistical advice was obtained. The Pearson chi-square test was used for analysis unless otherwise stated, and $P < 0.05$ taken to indicate significance.
laparoscopic nephroureterectomy, five (3%) had ureteroscopic resection of TCC and 12 (7%) had other procedures (anterior exenteration, distal ureterectomy or percutaneous treatment). Most patients with bladder TCC had a transurethral resection, 214 (10%) with muscle-invasive disease had a cystectomy, and the rest were treated with radiotherapy. Follow-up data were not evaluated.

Of the patients with upper urinary tract TCCs, 92 (56%) were found to have had a bladder TCC either before or after the diagnosis of the upper urinary tract lesion, 14 (8.5%) had synchronous bladder TCC, and 70 (43%) had metachronous bladder TCCs (data missing for the remaining eight patients). Tumours in the calyces or renal pelvis were found in 97 patients (59%), and 13 (8%), nine (6%) and 40 patients (24%) had TCC of the upper, mid and lower ureter, respectively. In 11 patients (7%) with ureteric tumours the site was not specified. Six patients (4%) had multifocal tumours, and are included in two of the above groups.

Table 1 shows the distribution of the grade and stage of TCCs. There were significant differences between the groups in tumour stage and grade; 35% of upper urinary tract TCC lesions were graded as G2 (moderately differentiated, low-grade) and 44% as G3 (poorly differentiated, high-grade), compared with only 31% and 35%, respectively, for patients with bladder TCC (P = 0.003). Of upper urinary tract lesions, 33% were stage pT2–T4 lesions compared with only 20% of bladder TCCs (P = 0.001). The incidence of high-grade deeply invasive disease was significantly higher in the upper urinary tract than in the bladder (Table 1). Correspondingly, the proportion of low-grade (G1 and G2) superficial (pTa/pT1) TCC was significantly higher in the bladder than in the upper urinary tract (P = 0.021).

There was an association between stage and grade in all cases (Pearson correlation coefficient, r = 0.7). Of all patients, 1229 (56%) had low-grade and pTa/pT1 disease, and 641 tumours (29%) were high-grade and deeply invasive. Only 217 patients (10%) with low-grade disease had deeply invasive tumours, and 123 (6%) had high-grade superficial tumours (P < 0.001). This relationship was the same when grade and stage of upper urinary tract and bladder TCC were analysed separately.

**DISCUSSION**

The anatomical location of upper urinary tract TCCs in the present study conforms with that described by Mazeman [2], who also reported that there were almost twice as many pelviccalyceal as ureteric tumours (60% and 40%, respectively, in the present study). Of the present patients with upper urinary tract TCC, 43% had metachronous bladder cancer, a proportion similar to that reported previously [14]. The pattern of pathology of the bladder tumours is consistent with standard teaching that 70% of tumours are superficial [1]. It is well established that 70% of superficial lesions present as stage pTa, 20% as pT1 and 10% as pTis, which was also reflected in the present findings. There was a strong correlation between grade and stage of TCC for both upper urinary tract and bladder TCCs; most low-grade tumours were noninvasive or superficially invasive, and high-grade tumours were predominantly deeply invasive (muscle or renal parenchyma), which is in good agreement with published data [6,8–12].

The main aim of the present study was to establish any differences in the pathology of TCC of the bladder and upper urinary tracts. Upper urinary tract TCC was significantly more aggressive and deeply invasive than TCC affecting the bladder. Although this has been alluded to previously, particularly in studies of patients with synchronous upper urinary tract and bladder TCC [5,17], this difference has not, until now, been well established. The more aggressive nature of upper urinary tract cancer might be a consequence of the higher-grade lesions found, or might represent anatomical differences between the bladder and ureter or renal pelvis and earlier transmural spread.

In the present study, 44% of upper urinary tract TCCs were grade G3; upper urinary tract TCC should therefore be regarded as an aggressive, high-grade cancer unless proven otherwise. These findings are important for managing upper urinary tract TCC, particularly as nephron-sparing procedures are redefining the management of these
lesions. Endourological techniques, which were until recently used for clearly defined situations (note above) are now more widely applied to patients with normal contralateral kidneys. However, indications for endourological management should be related to tumour rather than patient factors, i.e. small (<2.0 cm) solitary low-grade superficial lesions. Under these circumstances endourological management is safe and effective [14]. As upper urinary tract TCC appears to be potentially more aggressive than bladder tumours, a rigorous surveillance programme should be followed after initial conservative treatment. Patients must also be aware of the risk of recurrence and possible future requirement for nephroureterectomy [14]. Patients with multifocal disease, larger tumours, high-stage (pT2–T4) or grade 3 TCC should be offered nephroureterectomy [18], but the outcome after radical nephroureterectomy in patients with locally advanced disease (stage pT3–T4, N1–N2) is poor, with a 5-year survival rate of 23% [19]. In these patients, consideration might be given to adjuvant therapies such as local or systemic chemotherapy. However, these treatments have not been evaluated in prospective randomized trials, as this would be difficult given the low prevalence of upper urinary tract TCC [20].

The present study clearly shows that upper urinary tract TCC is a more aggressive tumour than that of the bladder. The clinical significance of this finding is important. If tumours of the upper urinary tract are automatically assumed to be of low grade and stage, as some reviews have suggested, and are fulgurated without previous biopsy, a patient with high-grade disease could potentially be denied curative surgery, in the form of a nephroureterectomy. Ureteroscopic biopsies should be mandatory if endourological management is to be used, as it cannot be assumed that TCC of the upper urinary tracts is of low grade and stage.

CONFLICT OF INTEREST

None declared.

REFERENCES


Correspondence: Mr S. Alan McNeill, Department of Urology, Western General Hospital, Edinburgh, EH4 2XJ, UK. e-mail: alan.mcneill@luht.scot.nhs.uk
The assessment of patient life-expectancy: how accurate are urologists and oncolgists?

JAMES R.M. WILSON, MICHAEL G. CLARKE, PAUL EWINGS, JOHN D. GRAHAM† and RUARAIDH MacDONAGH

Department of Urology, Taunton & Somerset Hospital, Taunton, and *Department of Oncology, Beatson Oncology Centre, Western Infirmary, Glasgow, UK

Accepted for publication 19 November 2004

OBJECTIVE

To assess the degree of accuracy, precision and consistency with which consultant urologists, oncolgists and junior doctors predict a patient’s 10-year life-expectancy.

SUBJECTS AND METHODS

Eighteen doctors of varying seniority independently examined 70 patient case scenarios containing detailed medical histories; 13 of these cases were duplicate scenarios. Bland-Altman analyses were used to compare doctors’ estimates of the probability of each hypothetical patient surviving 10 years with that calculated using actuarial methods. Intra- and interdoctor reliability were also assessed.

RESULTS

Compared with actuarial estimates, doctors underestimated the 10-year survival probability by an overall mean of 10.8% (95% confidence interval, 10.1–11.5%). The 18 individual doctors ranged from a mean underestimation of 33.2% to a mean overestimation of 3.9%. Variation around these means was considerable for each doctor, the standard deviations being 14.5–20.9%. Inter-doctor reliability was 0.58, while overall intra-doctor reliability was 0.74, but for individual doctors was 0.31–0.94. Junior doctors were less accurate in their predictions than the senior doctors. Five doctors tended to overestimate where life-expectancy was poor and underestimate where it was good.

CONCLUSIONS

Doctors were poor at predicting 10-year survival, tending to underestimate when compared with actuarial estimates. There was also substantial variability both within and between doctors. The inaccuracy, imprecision and inconsistency amongst the doctors in assessing patient life-expectancy is an important finding and has significant implications for managing patients. Many patients may be denied treatment after a pessimistic assessment of life-expectancy and (less commonly) some may inappropriately be offered treatment after an optimistic assessment. The particular inaccuracy in junior doctors compared with their senior colleagues also highlights the need for training. The development of a tool to assist in both training and clinical practice has the potential to improve doctors’ decision-making and patient care.

KEYWORDS

dife expectancy, comorbidty, actuarial, prostate cancer

INTRODUCTION

Treatment decisions for individual patients are based on several factors; in addition to the immediately relevant clinical variables, existing comorbidities and patient choice must also be considered [1]. The issue of life-expectancy can make the difference between patients receiving treatment and being denied it; e.g. current guidelines suggest that patients with localized prostate cancer should in general be offered curative treatment only if their estimated life-expectancy is >10 years [2]. However, multidisciplinary team meetings frequently only have clinical data available, and information on comorbidity, if presented at all, is often incomplete. Moreover, even when such information is available, it is unclear how well clinicians are able to translate factors such as family history, age and comorbidity into an estimate of life-expectancy. There is some evidence of an age bias, such that older patients are being offered curative treatments less frequently [3], and it has been suggested that this might arise from the clinicians’ inability to accurately assess patient life-expectancy [4].

To assess life-expectancy, incorporating a patient’s age and comorbidity is necessary; there are several measures for assessing comorbidity [5–8], but these are often too disease-specific to incorporate into wider clinical practice [9]. An example of a more generic measure is the Charlson score, the most widely used validated index [10,11]. This consists of 19 conditions, each allocated a weighting that equates to the relative risk of death, with an additional adjustment for age. This is easy to use and has been previously incorporated in the context of prostate cancer to predict survival [12,13], although it could be criticised for being developed in a relatively low-risk population. Of the other available generic measures, the Kaplan-Feinstein Index with its recent modification to produce the Adult Co-morbidity Evaluation-27, has generated most interest [14,15] and has been used in creating a combined head and neck comorbidity and pathological score [16]. An alternative system involves the use of actuarial data; the actuarial system, first proposed by Rodgers and Hunt in 1919, has been used by insurance companies for many years to estimate the perceived risks associated with policyholders [17]. Data are continually updated in line with available evidence and enable life-expectancy to be...
calculated on the basis of age, sex, smoking status, weight, blood pressure and other comorbid factors. Such information has been used to assess the accuracy of two consultant urologists in selecting for radical prostatectomy those patients with at least a 10-year life expectancy [18]. The notes of 261 patients, on whom they had previously performed radical prostatectomies for prostate cancer, were reviewed by the American General Life and Accident Insurance Company with subsequent calculation of the remaining life-expectancy for each patient on the basis of their comorbid factors, using actuarial data. About 20% of the patients who had undergone surgery had had a calculated life-expectancy of <10 years, suggesting some inaccuracy amongst clinicians in using comorbidity data to predict remaining life-expectancy.

Thus the aims of the present study were to assess the degree of accuracy, precision and consistency with which consultant urologists, oncologists and junior doctors predicted a patient’s 10-year life-expectancy, based on comorbid factors.

**SUBJECTS AND METHODS**

In all, 57 case scenarios were constructed to represent a realistic selection of patients seen in a general urology clinic. To assess consistency in estimating life-expectancy, 13 cases were repeated but distributed randomly, and consequently 70 case scenarios in all were presented to the clinicians. Each case included the patient’s age and medical history, e.g. a 66-year-old-man with poorly controlled insulin-dependent diabetes mellitus, diabetic retinopathy, hypertension and hypercholesterolaemia (Appendix). No details of any presenting condition were included.

Then 18 doctors, including four consultant urologists, two consultant oncologists, four urology specialist registrars, four surgical senior house officers (SHOs) and four surgical pre-registration house officers (PRHOs) were instructed to assign a probability of surviving 10 years (sometimes referred to as 10-year life-expectancy) for each of the 70 case scenarios. To represent the clinical and multidisciplinary team setting more accurately, the nature of the study and the use of patient scenarios were fully explained to all the participating clinicians. In addition, no time restraints were given and completion of the scenarios was supervised.

In collaboration with a professional actuary, actuarial tables were used to derive mortality ratios based on the comorbid factors for each case, using the actuarial ‘numerical rating system’, in which factors influencing mortality are represented by either a debit or credit score. The mortality of a ‘standard life’ (i.e. healthy patient with no comorbidity) is taken as 100%. Each comorbid factor has an associated additional mortality rating factor, expressed as a percentage of the standard life, e.g. sinus tachycardia with no organic cause; 96–100 beats per minutes (bpm) = no addition, 101–110 bpm = + 25%, 111–120 bpm = + 50% and >120 bpm = + 100%).

A sum total of these rating factors was calculated using a rating schedule, such that a comorbidity-attuned age was derived, e.g. a 65-year-old man with additional ratings of 100% has a comorbidity attuned age of 69 years [17].

The Charlson index [10] was then applied to the comorbidity-attuned age to derive a percentage chance of surviving 10 years. This approach circumvents the criticism that the Charlson index is only valid in a low-risk population, as the actuarial method has already been used to attune the age according to the comorbidities. In Charlson’s initial model the age score equated to 1 point per decade over 50 years, but this was adapted to allow an increase of 0.1 per single year of age.

The doctors’ predictions of 10-year survival were then compared with those calculated using actuarial figures, using ANOVA and Bland-Altman analyses. Differences between each prediction and the corresponding actuarial figure were calculated, and the mean (sd) of these differences derived for each doctor separately. Any propensity for a trend in these differences (e.g. underestimation when life expectancy is high and overestimation when life-expectancy is low) was examined using nonparametric correlation coefficients. The 13 repeated cases were used to assess intra-doctor reliability, and an overall inter-doctor reliability coefficient also calculated.

**RESULTS**

The 18 doctors assigned a percentage chance of 10-year survival for each of the 70 case scenarios. The patients were aged 55–82 years and the median (range) actuarial percentage chance of 10-year survival was 70 (5–94%). Compared with actuarial predictions, the doctors tended to underestimate the probability of 10-year survival, with considerable variability within and between doctors; this was particularly marked among the more junior doctors (Fig. 1); 15 doctors predominantly underestimated, with 10 underestimating over three-quarters of the cases.

The Bland-Altman plots and analyses confirmed the impression of underestimation, e.g. Fig. 2a shows such a plot for an SHO with an extreme tendency to underestimate. However, while many of the clinicians were relatively consistent in their underestimation (or, rarely, overestimation), the Bland-Altman plots for some clinicians suggested a more complicated picture, with a propensity to overestimate when the life-expectancy is low and underestimate when it is high (Fig. 2b).
Results of the Bland-Altman analyses for each clinician are shown in Table 1. The common propensity to underestimate is evident from the (mostly negative) mean differences between the clinician’s estimate and the actuarial figure for life-expectancy; the mean (range, 95% CI from a random-effects ANOVA) was $-10.8 (-33.2$ to 3.9, $-11.5$ to $-10.1$). By contrast, the SDs of the differences show relatively smaller variation (at 14.5–21.1), but the values are relatively large, i.e. all clinicians show considerable variation whatever their overall mean reflects in the way of under- or overestimation. The mean differences between the doctors’ estimates and the actuarial figures (Table 1) highlights in particular the inaccuracy in the predictions by SHOs and PRHOs compared with consultant urologists, oncologists and registrars.

Spearman’s correlation coefficients in Table 1 indicate a correlation between the differences (clinician’s estimate minus actuarial figure) and the level of life-expectancy (average of the two values); this confirms the impression from Bland-Altman plots that some clinicians are not consistent in their under- or overestimation. For example, registrar D had a significant negative correlation confirming the impression from Fig. 2b of overestimation when life-expectancy was low, and underestimation when it was high. Five clinicians had such a negative correlation, while one had a significant positive correlation, suggesting increasing overestimation with life-expectancy.

Results of test-retest (i.e. ‘intra-doctor’) reliability based on the 13 repeated cases showed a mixed picture, with considerable variation between clinicians (Table 1). Reliability coefficients were 0.31–0.94, with an overall intra-doctor reliability of 0.74. The inter-doctor reliability from these same 13 repeated cases was 0.58, similar to the 0.56 obtained for the 57 unique cases (i.e. ignoring the 13 repeats).

As a final illustration of the (in)accuracy of the doctors’ assessments, consider a situation where guidelines suggest that treatment should be proffered if the estimated probability of 10-year survival is $>50\%$. Using the actuarial estimates as a ‘gold standard’ it is possible to calculate the sensitivity and specificity of the doctors’ implied decisions. Of the 70 case scenarios, actuarial estimates would suggest treatment for 53 of them under this situation. For these 53 cases, the 18
doctors would on average recommend treatment for 66%, 'denying' treatment for 34%. Conversely, for the 17 cases that actuarial estimates would suggest withholding treatment, the doctors would on average concur in 76%, hence 'inappropriately' recommending treatment in 24%. If the threshold for recommending treatment is increased to 70% survival probability (where actuarial estimates would lead to treatment of half of the 70 cases), the sensitivity and specificity for the doctors' assessments would become 44% and 93%, respectively.

DISCUSSION

Even with detailed data on comorbidity, the clinicians in this study were generally inaccurate, imprecise and inconsistent in their predictions of patient 10-year survival, with an overall tendency towards underestimation. Junior doctors were generally less accurate in their predictions than their senior colleagues. In addition, several doctors appeared to overestimate where 10-year survival was poor and underestimate where it was good.

Relatively few doctors were assessed but more (and more varied) case scenarios were used than in previous studies. In addition, although the use of case scenarios does not represent the true clinic setting, such 'paper representations' of real patients are frequently used in multidisciplinary meetings to enable treatment plans to be formulated, and indeed high correlations between the assessments made by clinicians based on both real and 'paper' patients were identified previously [19]. It is inevitable that clinicians are more knowledgeable about outcomes in conditions directly relevant to their specialty; thus cardiologists (for example) may have been better at assessing life-expectancy than the clinicians in this study, because of the generic nature of the comorbidities presented. However, whenever treatment decisions relating to a presenting condition are influenced by assessing life-expectancy, these generic comorbidities are essential in such an assessment and need to be understood by a broad range of clinicians.

The findings have important implications for managing conditions where perceived life-expectancy influences treatment options and patient choice. The implication is one of potentially inappropriate management of some patients, with perhaps as many as 34% of patients in this study denied curative treatment based on a pessimistic assessment of life-expectancy, and 24% undergoing inappropriate treatment based on an optimistic view of life-expectancy.

The variability among doctors in the extent to which they either underestimated or overestimated 10-year survival also has clinical implications. Presentation of treatment options to an individual patient might well vary according to doctors' assessments of life-expectancy. Moreover, the inconsistency in many of the individual doctors when assessing the 13 repeat cases suggests that treatment decisions may also vary daily, even when patients are seen by the same consultant. Although many treatment decisions are now discussed in the multidisciplinary team setting and this might reduce variability, the decision will still be influenced by the overall tendency of the majority of clinicians present; this study suggests that that tendency might generally be one of pessimism about life-expectancy.

The general tendency to underestimate implies that some patients with good life-expectancy may be denied appropriate treatment, but also that the reverse (patients with a poor life-expectancy inappropriately being offered radical treatment) should be less common. However, the situation is potentially worse for the small group of clinicians who underestimate when life-expectancy is good and overestimate when it is poor, as this could result in both denial of treatment for patients with a good life-expectancy and inappropriate treatment if it is poor.

The particularly poor accuracy of the junior doctors (SHOs and PRHOs) raises the issue of training. Educating clinicians to more accurately assess life-expectancy should in principle be relatively straightforward, but this study highlights that experience alone is not enough, and suggests that applying comorbidity data is complex and difficult to learn and retain. Although senior doctors were better in their predictions, they still had a substantial degree of variability and inaccuracy, suggesting that training and education should be targeted at doctors of all levels.

Additional aids to assess life-expectancy could be useful in both the clinical and educational settings. The use of actuarial data, updated in line with current evidence-based literature, has the potential to provide an accurate source of information. The authors are currently engaged in developing a computer-based tool that could lead to improving the consistency and accuracy amongst clinicians of all seniority levels and specialties in their assessment of patient life-expectancy. The results of this study suggest that the scope for such improvement is considerable.

ACKNOWLEDGEMENTS

Funding: AstraZeneca provided funding for the input of a professional actuary and IT specialist (for the ongoing development of a software tool). The authors acted completely independently in the conduct of the study, over which AstraZeneca had no control.

Competing interests: the authors are currently engaged in the development of a software tool that will use actuarial data and techniques to assess life-expectancy based on the parameters for an individual patient. There is no intention that there would be any commercial gain from such a tool.

CONFLICT OF INTEREST

None declared.

REFERENCES

2 Royal College of Radiologists' Clinical Oncology Information Network British Association of Urological Surgeons. Guidelines on the management of prostate cancer. BJU Int 1999; 84: 987–1014
6 Greenfield S, Aronow HU, Elashoff RM, Watanabe D. Flaws in mortality data. the
15 http://www.oto.wustl.edu/clinepi/Forms/com_form.doc

Correspondence: James R.M. Wilson, Department of Urology, Taunton & Somerset Hospital, Musgrove Park, Taunton, TA1 5DA, UK. e-mail: jrmwilson@btopenworld.com

Abbreviations: SHO, senior house officer; PRHO, pre-registration house officer.

**APPENDIX**

<table>
<thead>
<tr>
<th>Age</th>
<th>Case</th>
</tr>
</thead>
<tbody>
<tr>
<td>57</td>
<td>42</td>
</tr>
<tr>
<td>74</td>
<td>43</td>
</tr>
<tr>
<td>67</td>
<td>44</td>
</tr>
<tr>
<td>69</td>
<td>45</td>
</tr>
<tr>
<td>74</td>
<td>46</td>
</tr>
</tbody>
</table>

PMH Insulin Dependent diabetic, blood sugar found to be 12, drinks more than 30 units per week, father died myocardial infarct at 56. Has mild calf pain walking up steep hills.

What do you believe is the percentage chance of this patient being alive at TEN years?

PMH Angina with Atrial Fibrillation, mild dyspnoea on exertion, slight cardiomegaly on chest x-ray, blood pressure found to be 165/90.

What do you believe is the percentage chance of this patient being alive at TEN years?

PMH Mild asthma

What do you believe is the percentage chance of this patient being alive at TEN years?

PMH Lower Urinary Tract Symptoms, femoral-popliteal bypass for peripheral vascular disease 2 years ago, currently asymptomatic, blood pressure 165/85 and smokes 5 cigarettes per day.

What do you believe is the percentage chance of this patient being alive at TEN years?

PMH Lower Urinary Tract Symptoms, blood pressure found to be 170/90, also has mild gout.

What do you believe is the percentage chance of this patient being alive at TEN years?
Towards a better understanding of involuntary detrusor activity

HELEN D. BRADSHAW, STEPHEN C. RADLEY*, DEREK J. ROSARIO† and CHRISTOPHER R. CHAPPLE†
Departments of Urology Research, *Obstetrics and Gynaecology, and †Urology, Sheffield Teaching Hospitals, UK
Accepted for publication 6 December 2004

OBJECTIVES
To compare the measured variables of involuntary detrusor activity (IDA) during ambulatory cystometry (AC) in women with and with no overactive bladder symptoms, and to evaluate the correlation between these variables and symptom severity.

PATIENTS AND METHODS
In all, 61 symptomatic and 39 asymptomatic women completed the Bristol Female Lower Urinary Tract Symptoms Questionnaire (BFLUTS-Q) and underwent AC. Measured variables of IDA (amplitude, duration, bladder volume and symptoms) were compared in the two cohorts.

RESULTS
IDA was detected in 47 of 61 symptomatic women (77%) and in 17 of 36 (47%) controls (P ≤ 0.01). The maximum IDA (defined as the highest amplitude contraction in any fill-void cycle) occurred at significantly lower volumes (328 vs 450 mL, P ≤ 0.05), was of higher amplitude (26 vs 12 cmH₂O, P = 0.14) and longer duration (83 vs 14 s, P ≤ 0.05) in symptomatic women than in controls. There was coincident incontinence in 22 (36%) symptomatic women and no controls (P ≤ 0.01). Discriminatory levels for clinically relevant IDA were established, and when applied retrospectively, classified 35 of 61 symptomatic women (55%) and one control (3%) as having such IDA. The correlation between symptom severity (measured by the BFLUTS-Q) and urodynamics was higher when these criteria were applied (r = 0.52 vs 0.38, P ≤ 0.01).

CONCLUSION
There are quantifiable differences between IDA found during AC in symptomatic and asymptomatic women. The measured variables of IDA may be useful to determine its clinical relevance, which may be indicated by contractions associated with leakage or contractions of >30 s occurring at bladder volumes of <300 mL.

KEYWORDS
detrusor overactivity, overactive bladder, ambulatory urodynamics

INTRODUCTION
The poor correlation between LUTS and conventional urodynamic findings has been well documented [1]. Despite individual laboratory cystometric (LC) measurements not being clinically useful in quantifying detrusor overactivity, and the tests’ apparent lack of sensitivity [2], the method is still commonly held to be a reliable and objective measure of detrusor function [3–5]. Ambulatory cystometry (AC) uses principles derived from established urodynamic practice.
but has the theoretical advantages of natural bladder filling, a longer period of observation and a relatively normal environment. The higher detection of involuntary detrusor activity (IDA) in symptomatic individuals may reflect more physiological lower urinary tract function during AC [6–8]. However, the detection of IDA in a large proportion of apparently healthy asymptomatic individuals during AC casts doubt on the clinical relevance of this finding [9,10].

The present study was designed to test the hypothesis that IDA detected during AC in symptomatic individuals is quantitatively distinct from IDA observed in healthy, asymptomatic volunteers. We also wished to determine which variables might be usefully employed to establish the characteristics of clinically relevant IDA (CRIDA).

PATIENTS, SUBJECTS AND METHODS

In all, 104 women referred for investigation of urgency, frequency and/or urge incontinence were recruited from gynaecology and urology outpatient clinics and underwent AC and LC. Women found to have urodynamic stress incontinence during LC were excluded from further analysis. A control group of 39 healthy volunteers was recruited by local advertisement. Controls were excluded if they reported bothersome urgency, frequency or any urge incontinence on the Bristol Female Lower Urinary Tract Symptoms Questionnaire (BFLUTS-Q) which all women completed before undergoing AC, according to a standard protocol [7,11]. Women with AC studies of inadequate quality for interpretation were excluded from further analysis. Methods, definitions and units conform to the standards recommended by the ICS unless otherwise stated.

AC was carried out using micro-tip pressure transducers mounted on silicone-coated 7 F catheters (Gaetac Ltd, Isle of Skye, UK) which were inserted urethrally and rectally to measure intravesical and intra-abdominal pressure, respectively. The transducers were calibrated before each investigation and zeroed to atmospheric pressure before insertion. Pressure was sampled at 8 Hz using a solid-state recorder (UPS-2020, Medical Measurements Systems, MMS®, the Netherlands). Symptoms of urgency and urinary leakage were recorded by the subject using a contemporaneous diary and event markers on the ambulatory box. Subjects graded the severity of urgency as mild (+), moderate (+++) or severe (+++). To identify detrusor activity associated with voiding, the subject pressed a specific event marker on the ambulatory box before each void. Connection to the flow meter was also automatically recorded. The investigator independently documented the time of voids, interventions and events. Provocative testing with repeated coughs and cold-water hand-washing was carried out during the third hour of monitoring. During each ambulatory study the signal quality was assessed with regular cough tests and real-time monitoring of pressure.

At the end of each investigation, recorded data were downloaded onto a personal computer and analysed in conjunction with the event diary, independent of the subject. Sections containing artefacts that might mimic or mask true changes in detrusor pressure were excluded. All IDA detected during the filling phase was analysed along with the estimated bladder volume at that point and any recorded symptoms. The following variables were documented: the amplitude and duration of IDA detected during filling; the maximum bladder capacity for each fill-void cycle; coincident symptoms and urinary leakage; the bladder volume at which IDA occurred. The first involuntary contraction was defined as that seen at the lowest bladder volume, in any fill-void cycle. The maximum contraction was defined as that with the highest amplitude, in any fill-void cycles.

Voided volumes were measured and the residual urine volume estimated by ultrasonography at the beginning and end of each investigation. Pre-weighed pads were used to quantify urinary leakage during the test. The mean fill rate was calculated for each fill/void cycle as (voided volume + leaked volume + residualvolume) / time. This value was then used to determine the bladder volume at specific times during the study.

For the statistical analysis, IDA in the two groups was compared using tests for nonparametric data (Mann–Whitney U). Linear regression was used to explore the factors responsible for the variability between the cohorts, and the chi-squared test to compare differences between proportions of healthy volunteers and symptomatic subjects. The association between symptoms reported in the BFLUTS-Q and urodynamic variables was evaluated using Spearman’s correlation coefficient.

RESULTS

In all, 61 AC datasets from symptomatic women were included in the analysis. Of the original cohort of 104 symptomatic women, 41 were excluded because they had urodynamic stress incontinence detected during conventional LC and a further two had interpretable AC data. In all, 39 healthy volunteers were eligible and underwent AC; the AC traces in three were uninterpretable and were excluded from the analysis. The mean (SEM) age of the symptomatic and asymptomatic groups was 56 (1.9) and 34 (1.6) years, respectively.

The maximum cystometric capacity, fill rate, number of fill-void cycles and total duration of monitoring in symptomatic women and controls are shown in Table 1. In controls IDA was detected in 17 of 36 studies (47%), whereas in symptomatic women there was IDA in 47 of 61 studies (77%; P < 0.01, chi-square). This activity coincided with the recording of severe urgency in seven controls and 40 symptomatic women (P < 0.01, chi-square). No controls had any urinary incontinence, whereas 22 symptomatic women had leakage coincident with IDA (P < 0.01).

Table 1 also shows the characteristics of the first and maximum episodes of IDA detected in each cohort. The first episode of IDA was at significantly higher median bladder volumes (P < 0.001) and of lower amplitude and shorter duration in controls than in symptomatic women. Similarly, the maximum IDA was at significantly higher bladder volumes and of significantly shorter median duration (both P < 0.001) in controls than in symptomatic women.

Linear regression showed that the symptomatic status of the subject was an important factor in the variability of certain AC variables, i.e. the volume at which IDA first occurred and the amplitude and duration of the maximum activity (Table 2). Age was not a significant factor in the variability of any of the urodynamic variables other than the amplitude of maximum IDA, which was negatively correlated with increasing age.
The symptom of urgency in the BFLUTS-Q before AC was reported as ‘never’ by 25 controls. The remaining 11 (30%) reported occasional urgency that was ‘not a problem’. In six of these 11, IDA was detected during AC. All symptomatic women reported troublesome overactive bladder symptoms (urgency, frequency or/and urge incontinence). The symptom of urgency was reported in the BFLUTS-Q ‘occasionally’ by 13 symptomatic women, ‘sometimes’ by 19, ‘most of the time’ by 19 and ‘always’ by ten.

Figure 1A shows the cumulative frequency of IDA with increasing bladder volume in symptomatic women and controls. At any given bladder volume <800 mL, IDA was detected in a relatively smaller proportion of controls than symptomatic women. For example, at bladder volumes of ≤300 mL, the first IDA had occurred in 72% of symptomatic women and controls. At any given bladder volume, a larger proportion of controls than symptomatic women had a maximum contraction of ≤30 s in duration (71% of controls and 23% of symptomatic women).

TABLE 1 The total duration, fill rate, maximum bladder capacity, and first and maximum detrusor contractions during AC in controls and patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls</th>
<th>Symptomatic</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>36</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td>Median (IQ):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>total duration, min</td>
<td>177 (127–234)</td>
<td>180 (124–234)</td>
<td>0.64</td>
</tr>
<tr>
<td>Median (range):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N fill/void cycles</td>
<td>1 (1–3)</td>
<td>2 (1–3)</td>
<td>0.01</td>
</tr>
<tr>
<td>Median (IQ)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>max. bladder capacity, mL</td>
<td>600 (400–688)</td>
<td>425 (335–580)</td>
<td>0.05</td>
</tr>
<tr>
<td>fill rate, mL/min</td>
<td>3.8 (1.3–8.3)</td>
<td>4.7 (1.7–12.7)</td>
<td>0.40</td>
</tr>
<tr>
<td>Detrusor contractions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>17</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>First detrusor contraction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQ)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>volume, mL</td>
<td>400 (339–592)</td>
<td>205 (145–334)</td>
<td>0.001</td>
</tr>
<tr>
<td>amplitude, cmH2O</td>
<td>10 (7–17)</td>
<td>13 (6–25)</td>
<td>0.12</td>
</tr>
<tr>
<td>duration, s</td>
<td>13 (9–37)</td>
<td>40 (15–85)</td>
<td>0.03</td>
</tr>
<tr>
<td>Maximum detrusor contraction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>volume, mL</td>
<td>450 (357–625)</td>
<td>328 (190–450)</td>
<td>0.009</td>
</tr>
<tr>
<td>amplitude, cmH2O</td>
<td>12 (8–25)</td>
<td>26 (16–46)</td>
<td>0.14</td>
</tr>
<tr>
<td>duration, s</td>
<td>14 (9–70)</td>
<td>83 (40–140)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

*Mann–Whitney U-test; IQ, interquartile range.

The total duration, fill rate, maximum bladder capacity, and first and maximum detrusor contractions during AC in controls and patients

TABLE 2 Linear regression analysis evaluating the effect of type (control or symptomatic woman) and age on ambulatory cystometry parameters

<table>
<thead>
<tr>
<th>Type (control or symptomatic)</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coefficients</td>
<td>P</td>
</tr>
<tr>
<td>P</td>
<td>P</td>
</tr>
<tr>
<td>First detrusor contraction</td>
<td></td>
</tr>
<tr>
<td>Volume</td>
<td>0.419</td>
</tr>
<tr>
<td>Amplitude</td>
<td>−0.262</td>
</tr>
<tr>
<td>Duration</td>
<td>−0.221</td>
</tr>
<tr>
<td>Maximum detrusor contraction</td>
<td></td>
</tr>
<tr>
<td>Volume</td>
<td>0.216</td>
</tr>
<tr>
<td>Amplitude</td>
<td>−0.499</td>
</tr>
<tr>
<td>Duration</td>
<td>−0.409</td>
</tr>
</tbody>
</table>

The symptom of urgency in the BFLUTS-Q before AC was reported as ‘never’ by 25 controls. The remaining 11 (30%) reported occasional urgency that was ‘not a problem’. In six of these 11, IDA was detected during AC. All symptomatic women reported troublesome overactive bladder symptoms (urgency, frequency or/and urge incontinence). The symptom of urgency was reported in the BFLUTS-Q ‘occasionally’ by 13 symptomatic women, ‘sometimes’ by 19, ‘most of the time’ by 19 and ‘always’ by ten.

Figure 1A shows the cumulative frequency of IDA with increasing bladder volume in symptomatic women and controls. At any given bladder volume <800 mL, IDA was detected in a relatively smaller proportion of controls than symptomatic women. For example, at bladder volumes of ≤300 mL, the first IDA had occurred in 72% of symptomatic women and 17% of controls. The symptom of urgency in the BFLUTS-Q before AC was reported as ‘never’ by 25 controls. The remaining 11 (30%) reported occasional urgency that was ‘not a problem’. In six of these 11, IDA was detected during AC. All symptomatic women reported troublesome overactive bladder symptoms (urgency, frequency or/and urge incontinence). The symptom of urgency was reported in the BFLUTS-Q ‘occasionally’ by 13 symptomatic women, ‘sometimes’ by 19, ‘most of the time’ by 19 and ‘always’ by ten.

Figure 1A shows the cumulative frequency of IDA with increasing bladder volume in symptomatic women and controls. At any given bladder volume <800 mL, IDA was detected in a relatively smaller proportion of controls than symptomatic women. For example, at bladder volumes of ≤300 mL, the first IDA had occurred in 72% of symptomatic women and 17% of controls.

Figure 1B,C shows the cumulative frequency for amplitude and duration of the maximum IDA; a larger proportion of controls than symptomatic women had a maximum rise in detrusor pressure of ≤20 cmH2O in amplitude (70% and 30%, respectively). Similarly, a larger proportion of controls

DISCUSSION

In the present study, the detection of IDA during AC in 47% of asymptomatic women is comparable with rates reported in other series [8,10,12]. Such observations have previously cast doubt on the reliability of AC for evaluating detrusor function. However, we found statistically significant differences between the variables of IDA in symptomatic and asymptomatic women.

To eliminate artifactual changes in detrusor pressure which could have been erroneously interpreted as IDA, the interpretation of AC during the present study adhered to a strict protocol [as recommended by the ICS [13]]. Consequently, 5% of studies were rejected, a rate similar to that in other centres with experience of AC [12].

Although the incidence of overactive bladder symptoms is known to increase with age [14], detrusor contractility actually decreases and the amplitude of IDA might also be expected to decline [15]. This was supported by the multivariate analysis, which showed that the amplitude of maximum IDA was negatively correlated with increasing age.

When comparing symptomatic with asymptomatic women there were statistically significant differences in the duration of maximum IDA and the bladder volume at which IDA occurred, and these variables appeared to be independent of age. It is therefore apparent that discriminatory levels may be identified which, when combined, may be used to give an indication of the clinical relevance of IDA, and that such an approach may offer an easily applicable and practical system for the descriptive interpretation of ambulatory urodynamic studies.

For each variable the point of maximum difference between the cohorts can be identified on the cumulative frequency curves (Fig. 1). This point may be used empirically to indicate discriminatory levels that distinguish IDA in controls from that in symptomatic women. There were significant differences between the groups in the volume at which IDA occurred and the duration of IDA, therefore the following discriminatory levels.
were identified as being most useful in distinguishing the two cohorts; first IDA occurring at a bladder volume \( \leq 300 \text{ mL} \); duration of maximal IDA > 30 s.

Applying these criteria to define CRIDA retrospectively in the two cohorts, CRIDA was detected in 32 (55%) of symptomatic and one (3%) of the asymptomatic women, whereas before applying these criteria the respective IDA detection rates were 77% and 47%. The loss of urine when a subject is attempting to inhibit bladder emptying is clearly suggestive of a clinical problem, but may also have an impact on measurable detrusor variables; when IDA is associated with leakage, its amplitude and duration may be reduced [3]. Miller et al. [16] reported an inverse correlation between the frequency of urge incontinence and the amplitude of uninhibited contractions during LC, that they ascribed to the effect of urethral sphincteric deficiency. When urethral sphincter function is adequate, high-amplitude IDA can develop, but when inadequate, only low-amplitude IDA can be recorded. To limit the confounding effect of sphincteric insufficiency, women with urodynamic stress incontinence during LC were excluded from the present study. Therefore, in addition to the discriminatory levels described, it seems appropriate to classify any IDA associated with urinary incontinence as CRIDA. In the original cohort of 61 symptomatic women, 32 had CRIDA based on duration and bladder volume alone, and three additional patients who did not fulfill these criteria had associated leakage. Reclassifying these three as CRIDA resulted in 35 of the original cohort of 61 symptomatic women (58%) and one control having CRIDA. CRIDA defined in this way was strongly associated with troublesome overactive bladder symptoms reported in the BFLUTS-Q before the investigation (\( P \leq 0.01 \)) and improved the correlation between symptoms and the urodynamic diagnosis (any IDA, \( r = 0.38 \); CRIDA, \( r = 0.52 \), both \( P < 0.001 \)).

This study shows that IDA during AC is quantifiable and that its quantification improves the correlation with symptoms. It supports the theory of van Waalwijk van Doorn et al. [17] underlying the detrusor activity index, a scoring system which is based on logistic regression and uses several variables, including fluid intake, voided volume, and the frequency and duration of activity. The detrusor activity index is yet to find general application in clinical practice.

Aside from its complexity, the frequency and total duration of detrusor activity are difficult to measure reliably if a study is not of optimal quality in its entirety. Practical methods for interpreting ambulatory urodynamic traces must circumvent the fact that discrete sections of an investigation may be suboptimal, whilst striving to maintain objectivity and simplicity.

In conclusion, there are significant and quantifiable differences in the variables of IDA detected during AC in asymptomatic and symptomatic women. Activity occurring at high bladder volumes and of short duration is common in asymptomatic individuals and may thus represent a variation of normal. In practice, it appears that IDA may indeed be a normal occurrence at one end of a spectrum ranging from normal to pathological in terms of its measured variables and associated symptoms. Its more severe and clinically relevant form (CRIDA) may be identified by a duration of >30 s and bladder volume of

---

FIG. 1. Cumulative frequency charts for: A, volume; B, amplitude of maximum contraction; and C, duration of maximum contraction, in symptomatic women (red closed squares) and controls (green open circles).
<300 mL or associated leakage. We think that these findings will help to overcome the earlier controversy relating to the specificity of AC, and the use of discriminatory levels as described here may be of considerable practical value in this context. However, perhaps more importantly, the present study gives greater insight into normal and abnormal detrusor function during natural filling, and should be considered when evaluating cystometric findings in general. During medium fill LC, it is recognized that nonphysiological filling and the abbreviated nature of the test may affect the assessment of detrusor function [6–8,16]. In addition, the relatively rapid changes in bladder volume will further influence the measured variables of IDA, perhaps explaining the test’s inability to usefully quantify the overactive detrusor and to discriminate between the relevant and irrelevant, as appears to be possible using AC.

CONFLICT OF INTEREST

None declared.

REFERENCES

9 Heslington K, Hilton P. Ambulatory monitoring and conventional cystometry in asymptomatic female volunteers. BJOG 1996; 103 : 434–41
14 Milsom I, Abrams P, Cardozo L, Roberts RG, Thurhoff J, Wein AJ. How widespread are the symptoms of an overactive bladder and how are they managed? A population–based prevalence study. BJU Int 2001; 87 : 760–6
15 Resnick NM, Yalla SV. Detrusor hyperactivity with impaired contractile function. An unrecognized but common cause of incontinence in elderly patients. JAMA 1987; 257 : 3076–81

Correspondence: Helen D. Bradshaw, Department of Urology Research, J Floor, Royal Hallamshire Hospital, Sheffield, S10 2JF, UK.

e-mail: h.d.bradshaw@sheffield.ac.uk

Abbreviations: LC, AC, laboratory, ambulatory cystometry; (CR)IDA, (clinically relevant) involuntary detrusor activity; BFLUTS–Q, Bristol Female Lower Urinary Tract Symptoms Questionnaire.
The pharmacokinetics of 400 μg of oral desmopressin in elderly patients with nocturia, and the correlation between the absorption of desmopressin and clinical effect

GITTE M. HVISTENDAHL, ANDERS RIIS*, JENS P. NØRGAARD* and JENS C. DJURHUUS
Department of Clinical Experimental Research, Aarhus University Hospital, Aarhus, and *Ferring International Centre, Copenhagen, Denmark
Accepted for publication 26 November 2004

OBJECTIVE
To investigate the pharmacokinetic profile of oral desmopressin in elderly patients with nocturia, and to analyse any possible correlation between the absorption and clinical effect.

PATIENTS AND METHODS
In all, 32 patients were screened to determine the baseline number of nocturnal voids and the nocturia index; of these, 24 fulfilled the inclusion criteria and were enrolled for a pharmacokinetic evaluation of oral desmopressin 400 μg. A double-blind, randomized, placebo-controlled, crossover-effect evaluation period was then used to test the association between the absorption of desmopressin and pharmacodynamic effect. Serial plasma samples were collected for 8 h for a pharmacokinetic analysis of desmopressin. The pharmacodynamics after an equivalent oral dose before bedtime were assessed by measuring changes in the number of nocturnal voids, time to first nocturnal void and nocturnal diuresis, from placebo to active treatment.

RESULTS
There was a linear relationship between plasma desmopressin at 2 h after dosing and the area under the plasma concentration curve from 0 to infinity (Pearson’s ρ 0.923, P < 0.001). Women had a significantly higher plasma desmopressin concentration than men (P = 0.0012) and more adverse events. There was no correlation between plasma desmopressin at 2 h after dosing and the within-patient response in any of the effect variables. Generally, the number of nocturnal voids and nocturnal diuresis were half that with placebo. The time to the first nocturnal void was almost doubled compared with placebo.

CONCLUSIONS
There seems to be a relationship between gender, plasma level of desmopressin and the incidence of adverse events. Plasma desmopressin at 2 h after dosing cannot be used to predict the pharmacodynamic response, although desmopressin lowers the nocturnal diuresis and the number of nocturnal voids.

KEYWORDS
desmopressin, elderly, nocturia, pharmacology
the pharmacokinetic results for oral desmopressin were limited and inconclusive. The efficacy studies of desmopressin in nocturia have shown that doses of 400 μg are sometimes needed to obtain the full effect [10], although other studies claim that the pharmacodynamic response does not increase when the dose is increased from 200 to 400 μg [19].

Thus the aim of the present study was to investigate the pharmacokinetic profile of 400 μg of oral desmopressin in elderly men and women complaining of nocturia, and to analyse any possible correlation between the absorption of desmopressin and the pharmacodynamic effect.

PATIENTS AND METHODS

Thirty-two patients reporting a large nocturnal diuresis were screened; of these, 24 (15 men and nine women) fulfilled the inclusion criteria and were included in the study. The inclusion criteria were age ≥65 years, nocturia more than twice per night and a nocturia index of >1 (defined as the mean nocturnal urine volume during the screening period divided by the largest voided volume). The exclusion criteria were any clinical significant renal, hepatic, gastrointestinal, pulmonary, cardiovascular, endocrinological or neurological disorder, any significant symptoms from the urinary tract apart from nocturia, medical treatment with drugs known or suspected to interact with desmopressin, and diuresis during the screening period of >40 mL/kg body weight. The study was conducted according to the Declaration of Helsinki and ICH Good Clinical Practice. Each patient signed a statement of informed consent approved by the local Ethics Committee before entering the trial.

After giving informed consent the patients’ health was confirmed by a complete physical examination, including dipstick testing a urine sample, uroflowmetry and ultrasonography after voiding to exclude residual urine. The patients then entered a 1-week screening period, during which they were asked to register the time and volume of each day- and night-time void, and the time and volume of fluid intake for at least three 24-h cycles. For the remaining nights of the week, the time and volume of each nocturnal void, including the first morning void, were recorded. From the registered data the number of nocturnal voids and the nocturia index were calculated. After the screening period, patients who fulfilled the inclusion criteria were included in the trial.

The trial was in two parts, i.e. part A, a pharmacokinetic evaluation of one oral dose of desmopressin 400 μg, and part B, a randomized, placebo-controlled, crossover-effect evaluation period (Fig. 1). The patients received information to drink no more than enough to satisfy their thirst from 1 h before to 8 h after taking the drug. The intake of coffee, tea or caffeinated beverages and other diuretic liquids were standardized as much as possible during the study days.

On the day of the pharmacokinetic evaluation the patients arrived at the laboratory in the morning. The first blood sample (0 h) was taken just before drug administration and then at 0.5, 0.75, 1, 1.5, 2, 3, 4, 6 and 8 h afterward. A standardized lunch was served at 3 h and an afternoon snack at 7 h. To evaluate the effects the patients arrived at 18.00 hours and were hospitalized for 14 h on 3 consecutive days, followed by a 7–14-day wash-out period before entering the second period of 3 days; the daytime was spent as outpatients. Desmopressin or placebo was given during 3 nights each in a randomized crossover design. On the test nights drug intake was at a standardized bedtime at 23.00 hours. Only one blood sample to determine plasma desmopressin was taken at 2 h after drug administration. The time and volume of each nocturnal void, and the time and volume of the morning void, was registered. The time of rising in the morning was standardized to 07.00 hours.

Safety was assessed during the study, as measurements of serum sodium, weight, blood pressure and pulse, taken before drug administration and 8 h afterward. The patient was withdrawn from the trial if the serum sodium declined to <125 mmol/L or there was symptomatic hyponatraemia with water retention (e.g. weight increase, oedema), cerebral symptoms or convulsions. Other intolerable adverse events, as judged by the patient or by the doctor (e.g. persisting nausea, headache or tiredness, feeling sick), or significant protocol violations (e.g. high diuresis >40 mL/kg) led to withdrawal.

All blood samples for desmopressin analysis were stored immediately on ice and then centrifuged at 1550 g within 45 min of collection. The plasma fraction was obtained and stored in labelled tubes at −70°C pending desmopressin analysis at the Department of Bioanalytical Chemistry, Ferring AB, Denmark, using a validated radioimmunoassay method. The lower limit of quantification for human plasma was 2.50 pg desmopressin/mL plasma. The mean intra- and interassay coefficients of variation of spiked human EDTA-plasma at 5, 10 and 100 pg/mL was 10.1%, 7.0% and...
The response was defined as a volume or baseline nocturnal diuresis. A dosing), baseline mean voided nocturnal voids) and absorption (2–3 h after intake) of desmopressin were calculated using the linear trapezoidal method and AUC, extrapolated to infinity (AUC_\text{inf}) according to the following equation:

\[ \text{AUC}_\text{inf} = \text{AUC} + \frac{C_\text{last}}{\lambda_z} \]

where C_\text{last} denotes the last measurement for the patient in question and \lambda_z the estimated slope from a log-linear regression on the last measurements from the patient in question. The terminal half-life was calculated as 

\[ t_{1/2} = \ln(2)/\lambda_z \]

where the values in the tail of the curve where the transformed concentrations seem to follow a linear elimination rate were used. A descriptive statistical analysis, e.g. geometric mean and corresponding percentage coefficient of variation, median and range, and harmonic mean with corresponding interquartile range, was generated for the pharmacokinetic variables. The correlation between one plasma desmopressin value 2–3 h after intake and \text{AUC}_\text{inf} was assessed graphically and using Pearson’s correlation coefficients with corresponding 95% CI. A logistic regression analysis was used to describe correlations between the response (reduction in number of nocturnal voids) and absorption (2–3 h after dosing), baseline mean voided nocturnal volume or baseline nocturnal diuresis. A response was defined as a ≥25% reduction in the number of nocturnal voids from placebo treatment. Pearson’s and Spearman’s correlation coefficients were calculated to detect any pairwise correlation between absorption and the desmopressin-placebo difference in time to first void and the desmopressin-placebo reduction in nocturnal diuresis. Descriptive statistics, e.g. median and range, were calculated for the effect variables, with the level of significance set at \( P < 0.05 \).

**RESULTS**

Finally 23 patients were included in the analysis of pharmacokinetics, as one was excluded because of protocol violations; in the pharmacodynamic part (A), 24 were included and analysed. The mean (SD) age of the included patients was 71.7 (6.5) years and the body weight 75.1 (11.3) kg. Eleven drug-related adverse events were reported during desmopressin treatment and one with placebo. Four patients, all women, were withdrawn from part B because of adverse events related to low serum sodium values. There were no serious adverse events during the study. The most common adverse events reported were hyponatraemia (below normal range), headache and weight increase (>2%) of the initial body weight). All but one adverse event after desmopressin treatment were in the women. Six of the nine women had a weight gain of >2% from baseline the serum sodium was checked before giving the next dose.

**TABLE 1 Serum sodium values for the nine women during placebo/desmopressin treatment. The values in italics represent those women with no clinically relevant changes in serum sodium below normal range (136–146 mmol/L). Serum sodium was measured before the first dose and 8 h afterward. If the patient had a weight gain of >2% from baseline the serum sodium was checked before giving the next dose.**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Placebo</th>
<th>Desmopressin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dose I</td>
<td>Dose II</td>
</tr>
<tr>
<td>1</td>
<td>137/140</td>
<td>/138/137</td>
</tr>
<tr>
<td>2</td>
<td>143/142</td>
<td>/142/141</td>
</tr>
<tr>
<td>3</td>
<td>142/142</td>
<td>/142/141</td>
</tr>
<tr>
<td>4</td>
<td>139/141</td>
<td>/141/141</td>
</tr>
<tr>
<td>5</td>
<td>141/141</td>
<td>/142/141</td>
</tr>
<tr>
<td>6</td>
<td>139/139</td>
<td>/141/139</td>
</tr>
<tr>
<td>7</td>
<td>137/139</td>
<td>/140/139</td>
</tr>
<tr>
<td>8</td>
<td>138/141</td>
<td>/141/140</td>
</tr>
<tr>
<td>9</td>
<td>ex/ex</td>
<td>ex/ex</td>
</tr>
</tbody>
</table>

ex, excluded; a, 18.00 hours; b, 07.00 hours.

**FIG. 2.**

The desmopressin plasma concentrations with time for all 24 patients, with the mean (SD) superimposed.
plasma desmopressin at 2 h after dosing and AUC\textsubscript{inf} was 0.923 (0.824–0.967) (P < 0.001). The relationship between AUC\textsubscript{inf} and desmopressin concentration at 2 h is shown in Fig. 4 (AUC\textsubscript{inf} = 6.36 ¥ desmopressin + 1.73).

Of all 23 patients, 13 (57%) were responders (nine men and three women). The response could not be significantly predicted by the plasma desmopressin level 2–3 h after dosing or baseline mean voided nocturnal volume. There was no correlation between the desmopressin – placebo difference in time to first void and absorption, or as desmopressin – placebo difference in nocturnal diuresis and absorption, with r\textsubscript{Spearman} of −0.01 (P = 0.531) and 0.06 (P = 0.612), respectively.

The mean number of nocturnal voids was less on desmopressin than placebo, the mean time from drug intake to first micturition significantly higher (P = 0.0261), and the mean nocturnal diuresis significantly lower (P < 0.001; Table 4). The baseline median nocturnal voided volume decreased during desmopressin treatment by 60 (−213 to 55) mL.

**DISCUSSION**

One of the aims of the present study was to investigate the pharmacokinetic profile of one dose of oral desmopressin in elderly men and women. The relatively high dose was chosen based on a previous pharmacokinetic study in elderly men (unpublished data), where low plasma levels of desmopressin only gave limited information on the pharmacokinetics in this age group. The elderly were chosen as they represent a large group with a medical problem that may be resolved by treatment with desmopressin. Studies on LUTS show that 72% of elderly people have nocturia and find it very bothersome [5,20]. Furthermore, the elderly may have different patterns of absorption and elimination of drugs. Based on the data from this study, the AUC\textsubscript{inf} strongly depends on the plasma desmopressin concentration at 2 h after dosing. Theoretically it is possible that the pharmacokinetic characteristics may differ with different doses, which makes it difficult to apply this model to other age groups or other doses of desmopressin. Surprisingly, the desmopressin plasma levels in the women were higher than in the men; when adjusting the AUC\textsubscript{inf} for body weight the difference persisted. This is clinically important and illustrates that extra care is required when elderly women are treated with desmopressin. The plasma level of desmopressin was still over the lower limit of quantification 8 h after drug intake in 16 of the 23 patients, indicating that in these elderly patients desmopressin may have had a long duration of action at this specific dosage. For treating nocturia, a duration of 6–8 h is sufficient. A longer duration is unwarranted because of the risk of water retention and related adverse events. Even though the mean serum sodium level for the whole group was rather stable during the 3 days of desmopressin treatment, most of the women had a decrease in sodium level below the normal range. This may have been incidental, but it suggests that these women were dosed above the therapeutic range and supports the suspicion of an overly long duration of action. In a recent desmopressin dose-titration study in men, serum sodium levels below the normal range were reported in 22% of the patients and 4% had serum sodium levels of <130 mmol/L [10]. Furthermore, patients at the highest risk of developing hyponatraemia were those aged ≥65 years. Similar adverse events were reported in other studies of desmopressin treatment in elderly patients [6].

**TABLE 2 Mean plasma desmopressin pharmacokinetic variables after one oral dose of 400 μg for all patients and for men and women**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Geometric mean (95% CI)</th>
<th>% Coefficient of variation</th>
<th>Harmonic mean (95% Hodges-Lehman CI)</th>
<th>Median (interquartile range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC\textsubscript{t}</td>
<td>63.1 (49.6–80.2)</td>
<td>60.2</td>
<td>–</td>
<td>55.4 (47.7–84.8)</td>
</tr>
<tr>
<td>AUC\textsubscript{inf}</td>
<td>79.1 (61.9–101.2)</td>
<td>61.9</td>
<td>–</td>
<td>70.7 (62.3–106.5)</td>
</tr>
<tr>
<td>C\textsubscript{max}</td>
<td>16.0 (12.7–20.2)</td>
<td>58.2</td>
<td>–</td>
<td>14.2 (11.6–22.6)</td>
</tr>
<tr>
<td>t\textsubscript{1/2}</td>
<td>–</td>
<td>–</td>
<td>3.1 (2.9–3.6)</td>
<td>3.3 (2.7–3.8)</td>
</tr>
<tr>
<td>t\textsubscript{max}</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1.5 (1.0–2.0)</td>
</tr>
</tbody>
</table>

FIG. 3. Individual desmopressin profiles in women (A) and men (B).
The pharmacodynamic study was intended to determine whether the response (as the difference in the number of nocturnal voids) was predicted by absorption 2 h after drug intake. There was a clear reduction in the number of nocturnal voids, significantly reduced nocturnal diuresis and significantly increased time to first void during desmopressin treatment, matching results from other studies [7], but there was no clear association between absorption and response in any of the variables analysed. Interestingly, the men had a longer median time to first void than women after desmopressin (Table 4). However, the groups were small and the range in each group very large, which may explain the difference. Differences in nocturnal bladder capacity and sleep quality may also influence the results.

The lack of association between response and absorption might be explained by the high dose the patients were given. The plasma levels of desmopressin achieved in this study group were probably much higher than the threshold for anti-diuretic action, which contradicts the previously cited study [10]. However, they conducted a dose-titration based on the dynamic response, whereas the present patients all received the same dose of desmopressin. Apart from a large inter-individual variation in the plasma desmopressin at 2 h the patients had a large intra-individual variation apparently with no effect on the response variables. This study shows that high doses of desmopressin primarily increase the duration of action and not the response.

In conclusion, the present results indicate clearly that the AUC\textsubscript{inf} strongly depends on the plasma level at 2 h after dosing with 400 \( \mu \)g of oral desmopressin, suggesting that in future studies it might be possible to characterize the absorption/elimination of the drug using only a few blood samples. There seems to be a relationship between gender, plasma desmopressin and the incidence of adverse events. Therefore, care should be taken when treating elderly women with desmopressin. Desmopressin about halved the number of nocturnal voids and nocturnal diuresis. The time to first void was higher on desmopressin and the nocturia index was halved on desmopressin. There was no correlation between response and plasma concentrations during oral treatment with 400 \( \mu \)g desmopressin. Further studies are needed to determine if this will occur with lower doses of desmopressin.

ACKNOWLEDGEMENTS

The authors thank Ferring Pharmaceuticals for financial support.

CONFLICT OF INTEREST

A. Riis is a statistician at Ferring Pharmaceuticals. J.P. Nørgaard is a medical director and scientific officer.

REFERENCES

1 Vilhardt H. Basic pharmacology of Desmopressin: a review. Drug Invest 1990; 2 (Suppl. 5): 2–8


14 Vilhardt H, Lundin S. Biological effect and plasma concentrations of DDAVP after intranasal and per oral administration to humans. General Pharmacol 1986; 17: 481–3


Correspondence: Gitte M. Hvistendahl, Institute of Experimental Clinical Research, Aarhus University Hospital-Skejby, Dk-8200 Aarhus N, Denmark.
e-mail: g.hvistendahl@dadinet.dk

Abbreviations: AUC, area under the curve.
Self-assessed health, sadness and happiness in relation to the total burden of symptoms from the lower urinary tract

GABRIELLA ENGSTRÖM*†‡, LARS HENNINGSOHN§¶ and JERZY LEPPERT†

*Uppsala University, Department of Public Health and Caring Sciences, Uppsala Science Park, Uppsala, Sweden, †Centre for Clinical Research, Uppsala University, Central Hospital, Västerås, Sweden, §Department of Caring Sciences and Public Health, Mälardalen University, Västerås, Sweden, Clinical Cancer Epidemiology, Department of Oncology-Pathology, Karolinska Institutet, Stockholm, Sweden, ¶Division of Urology, Centre for Surgical Sciences, Karolinska Institutet, Stockholm, Sweden

Accepted for publication 15 November 2004

OBJECTIVES

To evaluate the effect of lower urinary tract symptoms (LUTS) on self-assessed health, sadness and happiness of men.

SUBJECTS AND METHODS

The study included 504 men (aged 40–80 years) in the rural community of Surahammar, Sweden, who a year earlier had reported stress incontinence, urgency or postvoid dribbling in answer to a postal questionnaire, and 504 age-matched control men from the same community. The occurrence of 12 specific LUTS was rated using the Danish Prostatic Symptom Score. Health, sadness and happiness were measured by three questions from the Medical Outcomes Study Short-Form 36 health survey questionnaire.

RESULTS

Completed questionnaires were returned by 74.2% of men (748/1008). A low score for health was reported by 34% of men with one to four LUTS, by 67% with five to eight, and by 75% with nine or more LUTS. The total LUTS burden correlated with lower scores for happiness and with higher scores for sadness. For each of the 12 specific LUTS, men with the symptom had lower scores for health and happiness, and higher scores for sadness, than men without the symptom. Comparing men with the symptom of ‘other incontinence’ to men with no ‘other incontinence’, the relative risk (95% confidence interval) of impaired health was 2.2 (1.8–2.8), while that of a high score for happiness was 0.5 (0.3–0.7) and that of greater sadness was 2.3 (1.7–3.3). Social status, marital status, education, smoking, physical activity and urinary tract infection all affected the impact of LUTS.

CONCLUSIONS

The total burden of LUTS is related to self-assessed health, sadness and happiness.

KEYWORDS

health, sadness, happiness, DAN-PSS, lower urinary tract symptoms, SF-36

INTRODUCTION

LUTS affect self-assessed quality of life (QoL), in the last decade, the traditional way of measuring urinary symptoms (frequency, severity) has been supplemented by questions relating to the symptom of individual distress [1], as well as a sense of well-being and self-assessed QoL. [2–6]. A quick evaluation of the discomfort caused by LUTS and improvements in QoL is an important goal [7], as different treatment strategies depend on symptom quality and distress, and one major therapeutic goal is to improve the QoL of affected men. To our knowledge, no published study has reported the effect on QoL in relation to the number of LUTS in men. In the present study, we evaluated factors related to QoL, and the LUTS burden in correlation with self-assessed health, sadness and happiness. This information could be useful for more effective therapeutic decisions.

SUBJECTS AND METHODS

The study was conducted in the rural community of Surahammar, Sweden, where, in 1997, the 11 200 inhabitants included 2571 men aged 40–80 years. All of the men invited to take part had participated a year earlier in a self-administered questionnaire study (yes or no) investigating the prevalence of three common LUTS, i.e. stress incontinence, urgency and post micturition dribbling [1]. All 504 men who had reported one or more LUTS were invited to take part in the present study. As a control group, 504 randomly selected men from the same community who had reported no LUTS in the previous study were matched by age to the group that had reported LUTS, and they were also invited to participate (Fig. 1). These 1008 men were all sent a letter of invitation explaining the objectives of the study, and a postal reminder was sent twice to those who did not reply within 4 and 6 weeks.

The respondents completed a self-administered questionnaire, the Danish Prostatic Symptom Score (DAN-PSS [6], comprising 12 questions relating to LUTS), and three general questions about health, sadness and happiness, from the Swedish version of the Medical Outcomes Study Short-Form 36 health survey (SF-36) [8]. Information was also collected about potential confounding and effect-modifying factors, e.g. social status, education, marital status, smoking, physical activity and UTI during the preceding year.

In the DAN-PSS, the severity or frequency of specific symptoms of LUTS were assessed on a four-category scale (no, mild, moderate, much). 'Urge incontinence', 'stress incontinence', 'other incontinence', hesitancy, incomplete emptying, straining, dysuria and urgency were classed as 'mild' when the symptom was reported to occur rarely, 'moderate' when the symptom occurred often and 'much' when the symptom occurred
always. 'Weak stream' was classed as 'mild' when the urinary stream was weak, 'moderate' when very weak, and 'much' when classified as dribbling. 'Daytime frequency' was classed as 'mild' when the interval between voids was 2–3 h, 'moderate' when 1–2 h, and 'much' when <1 h. 'Nocturia' was classed as 'mild' when it occurred once or twice at night, 'moderate' when three to four times, and 'much' when five or more times. 'Post micturition dribbling was classed as 'mild' when dribbling was reported only to take place in the lavatory, 'moderate' when a small amount of dribbling occurred in the trousers, and 'much' when a large amount of dribbling occurred in the trousers.

The questions that were used from the general SF-36 questionnaire [9] related to self-assessed health, sadness and happiness (Appendix 1). Outcome variables for the self-assessed health, sadness and happiness questions were dichotomised. The response relating to the health question was classed as 'low' if the answer was 'moderate' or 'bad'. Sadness was classed as 'high' if the answer was 'all of the time', 'most of the time', 'some of the time' or 'part of the time'. Happiness was classed as 'high', if the answer was 'all of the time' or 'most of the time' (Appendix 1).

For dichotomised symptom characteristics, the variables were classified as 'no symptom' or 'symptom'. To calculate relative risks (RRs), the percentage of men reporting a specific symptom was divided by the percentage of men reporting no levels of the same symptom. The RRs for background characteristics were calculated as the percentage of men with LUTS reporting the outcome divided by the percentage of men with no LUTS who reported the same outcome. The RR and 95% CI were calculated and proportions used to describe the number and percentage of men with specific LUTS. The ethics committee at Uppsala University approved the study.

RESULTS

In all, 748 (74.2%) men returned the questionnaire; a year earlier 411 of these men (55%) had reported stress incontinence, urgency or post micturition dribbling, and 337 (45%) had none of these symptoms. The mean (SD, range) age of the participants at the time of answering the questionnaire was 60 (10.7, 40–80) years. The characteristics of the cohort are shown in Table 1.

SELF-ASSESSED HEALTH

The risk of obtaining a low score for health was significantly higher in men with LUTS than in men with no LUTS for all the evaluated characteristics, except for unemployed men, men on sick leave and men with self-reported UTI. Employed men with LUTS had lower scores for health than employed men with no LUTS. For men who went to secondary school, the risk of a low health score was 10 times higher for those with LUTS than for men with no LUTS. Single or widowed men with LUTS reported the same effect on health as those with no LUTS (Table 2).

When each of the 12 specific LUTS were considered, the risk of a low score for health was higher for men with the symptom than for men without the symptom (Table 3). In particular, of men who experienced leakage of urine with no urge or physical activity ('other incontinence'), 59% reported a low score for health, compared with 26% of men who experienced no 'other incontinence'. The RR of a low score for health was 2.1 (1.7–2.6) for men with urge incontinence compared to men with no urge incontinence.

SELF-ASSESSED SADNESS

Of men who had studied at university, a high score for sadness was reported by 29% of men with LUTS, compared with 10% of men with no LUTS. Smokers with LUTS had a greater risk of obtaining a high score for sadness than smokers with no LUTS. Of men living as single/widowers, or married/living together, the RR of a high score for sadness in men with LUTS was higher than in men with no LUTS (Table 4).
The risk of a high score for sadness was significantly higher in men with each of 12 specific LUTS. 'Other incontinence' significantly increased the risk of feeling 'part of the time' or 'all the time' in men with 'mild', 'moderate' or 'much' effect from this symptom, compared with men unaffected by 'other incontinence'. The RR of a high score for sadness in men with stress or urge incontinence was 2.1 and 1.9, respectively. The risk of a high score for sadness was higher in men with 'mild', 'moderate' or 'much' effect from the symptom of post-micturition dribbling than in men unaffected by this symptom (Table 5).

SELF-ASSESSED HAPPINESS

All men apart from those on sick leave reported a significant effect on their happiness score if they had LUTS, compared with men with no LUTS (Table 4). All 12 LUTS significantly reduced the happiness score among men affected mildly, moderately or much compared with men with no LUTS. The proportion of men with a high score for happiness was lower among those who rarely, often, or always had leakage of urine without urge or physical activity than among those men who never had 'other' incontinence (Table 5). Stress incontinence significantly reduced the score for happiness in men with 'mild', 'moderate' or 'much' effect from this symptom compared with men unaffected by stress incontinence. The relative prevalence of high scores for happiness was 0.6 for men with 'mild', 'moderate' or 'much' urge incontinence compared with men without urge incontinence (Table 5).

SELF-ASSESSED HEALTH AND SYMPTOM BURDEN

A low score for health was reported by 30% (209 of 692) of the men (Table 6). The self-assessed health correlated with the total LUTS symptom burden. The relative risk of moderate or bad health, with 95% confidence intervals for social status, education, marital status, smoking, physical activity and urinary tract infection (UTI) in men with lower urinary tract symptoms vs. no lower urinary tract symptoms is shown in Table 2.
HEALTH, SADNESS AND HAPPINESS IN RELATION TO LUTS

Table 4: The RR of sadness ('all the time' or 'part of the time') and happiness ('all the time' or 'most of the time') for men with LUTS vs men with no LUTS

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Sadness, N/total (%)</th>
<th>RR (95% CI)</th>
<th>Happiness, N/total (%)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LUTS</td>
<td>No LUTS</td>
<td></td>
<td>LUTS</td>
</tr>
<tr>
<td>Social status:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employed</td>
<td>35/196 (18)</td>
<td>19/170 (11)</td>
<td>1.6 (0.9–2.7)</td>
<td>93/196 (47)</td>
</tr>
<tr>
<td>Retired</td>
<td>28/122 (23)</td>
<td>9/71 (13)</td>
<td>1.8 (0.9–3.6)</td>
<td>48/123 (39)</td>
</tr>
<tr>
<td>Unemployed</td>
<td>9/17 (53)</td>
<td>1/17 (6)</td>
<td>3.1 (0.5–20.1)</td>
<td>13/16 (19)</td>
</tr>
<tr>
<td>On sick leave</td>
<td>20/46 (43)</td>
<td>5/25 (20)</td>
<td>2.2 (0.9–5.1)</td>
<td>9/45 (20)</td>
</tr>
<tr>
<td>Education:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary school</td>
<td>63/246 (26)</td>
<td>24/164 (15)</td>
<td>1.1 (1.1–2.7)</td>
<td>105/245 (43)</td>
</tr>
<tr>
<td>Secondary school</td>
<td>11/76 (14)</td>
<td>5/65 (8)</td>
<td>1.8 (0.7–5.1)</td>
<td>31/77 (40)</td>
</tr>
<tr>
<td>University studies</td>
<td>16/66 (29)</td>
<td>4/41 (10)</td>
<td>2.9 (1.1–8.1)</td>
<td>18/56 (32)</td>
</tr>
<tr>
<td>Marital status:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single/widower</td>
<td>26/62 (42)</td>
<td>6/38 (16)</td>
<td>2.6 (1.2–5.8)</td>
<td>16/63 (25)</td>
</tr>
<tr>
<td>Married/living together</td>
<td>66/323 (20)</td>
<td>28/237 (12)</td>
<td>1.7 (1.1–2.6)</td>
<td>138/322 (43)</td>
</tr>
<tr>
<td>Other:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>27/77 (35)</td>
<td>65 (10)</td>
<td>3.5 (1.5–7.7)</td>
<td>32/76 (42)</td>
</tr>
<tr>
<td>Non-smoker</td>
<td>63/308 (21)</td>
<td>28/217 (13)</td>
<td>1.6 (1.1–2.5)</td>
<td>122/309 (39)</td>
</tr>
<tr>
<td>Physical activity, ≤ twice/week</td>
<td>50/209 (24)</td>
<td>20/137 (15)</td>
<td>1.6 (1.0–2.6)</td>
<td>75/208 (36)</td>
</tr>
<tr>
<td>Physical activity, &gt; twice/week</td>
<td>41/175 (23)</td>
<td>14/138 (10)</td>
<td>2.3 (1.3–4.0)</td>
<td>79/176 (45)</td>
</tr>
<tr>
<td>UTI</td>
<td>13/38 (34)</td>
<td>0/6</td>
<td>–</td>
<td>7/38 (18)</td>
</tr>
<tr>
<td>No UTI</td>
<td>80/346 (23)</td>
<td>34/269 (13)</td>
<td>1.8 (1.3–2.6)</td>
<td>147/346 (42)</td>
</tr>
</tbody>
</table>

Table 5: The RR of sadness and happiness for men for a specific LUTS vs men without that specific symptom

<table>
<thead>
<tr>
<th>DAN-PSS item</th>
<th>Sadness, N/total (%)</th>
<th>RR (95% CI)</th>
<th>Happiness, N/total (%)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other incontinence*</td>
<td>29/75 (39)</td>
<td>96/583 (17)</td>
<td>2.3 (1.7–3.3)</td>
<td>20/77 (26)</td>
</tr>
<tr>
<td>Stress incontinence</td>
<td>26/71 (37)</td>
<td>101/587 (17)</td>
<td>2.1 (1.5–3.0)</td>
<td>18/72 (25)</td>
</tr>
<tr>
<td>Urgency</td>
<td>48/159 (30)</td>
<td>78/500 (16)</td>
<td>1.9 (1.4–2.7)</td>
<td>50/160 (31)</td>
</tr>
<tr>
<td>Nocturia</td>
<td>90/364 (25)</td>
<td>37/295 (13)</td>
<td>1.9 (1.4–2.8)</td>
<td>145/365 (40)</td>
</tr>
<tr>
<td>Weak stream</td>
<td>82/365 (23)</td>
<td>46/295 (16)</td>
<td>1.4 (1.0–2.0)</td>
<td>153/366 (42)</td>
</tr>
<tr>
<td>Daytime frequency</td>
<td>64/286 (22)</td>
<td>64/375 (17)</td>
<td>1.3 (1.0–1.8)</td>
<td>121/286 (42)</td>
</tr>
<tr>
<td>Incomplete emptying</td>
<td>77/330 (23)</td>
<td>46/325 (14)</td>
<td>1.7 (1.2–2.3)</td>
<td>132/330 (40)</td>
</tr>
<tr>
<td>Dysuria</td>
<td>37/110 (34)</td>
<td>90/548 (16)</td>
<td>2.0 (1.5–3.2)</td>
<td>32/109 (29)</td>
</tr>
<tr>
<td>Post micturition dribbling</td>
<td>107/471 (23)</td>
<td>21/189 (11)</td>
<td>2.0 (1.3–3.2)</td>
<td>199/472 (42)</td>
</tr>
<tr>
<td>Straining</td>
<td>70/308 (23)</td>
<td>58/353 (16)</td>
<td>1.4 (1.0–1.9)</td>
<td>120/309 (39)</td>
</tr>
</tbody>
</table>

*Urinary leakage without urge or physical activity.

Overall, 19% (128 of 662) of the men felt sadness ‘all of the time’ or ‘part of the time’. Among men unaffected by LUTS, 12% reported sadness, vs 43% of men with 5–8 LUTS. There was no further significant increase in reported sadness in men with 9–12 LUTS (Table 6). The RR of a high score for sadness in men with one or more LUTS was 2.0 (1.4–2.8).

Discussion

The symptom burden from LUTS determines self-assessed health, sadness and happiness. Most LUTS that were measured in the present study by the DAN-PSS (12 symptoms) had a negative effect on these factors, and there was a strong correlation between the number of LUTS reported and self-assessed health and happiness. A significant difference was already apparent in men affected by one LUTS.
[RR 1.5], and the prevalence of a low score for health continued to increase with up to eight LUTS. The prevalence of a high score for happiness decreased and that of a high score for sadness increased in the same way, associated with increased LUTS burden. These data are supported by studies of self-assessed variables of well-being. Henningssohn et al. [10] reported that the number of chronic symptoms after treatment for urinary bladder cancer determines the risk of a lower self-assessed well-being, while Koskimäki et al. [6] reported that reduced health was associated with an increased LUTS impact, as measured using the DAN-PSS questionnaire. Correlations have also been found when the impact of LUTS was measured by other methods, e.g. the IPSS [11,12].

In the present study, symptom severity was associated with negative effects on self-assessed health, sadness and happiness. Other studies have also shown negative effects of increasing symptom severity on different QoL domains [SF-36 and King’s Health Questionnaire] [4,6,13], thus it appears that the same effect can be measured by extracting key questions from the more extensive QoL questionnaires that are often used.

Different LUTS affect self-assessed health, sadness and happiness in different ways. ‘Other’ incontinence and urge incontinence appear to have a greater impact on health than stress incontinence. In another population-based Swedish study by Hägglund et al. [14], urge incontinence had a greater effect on QoL than stress incontinence in women. It is reasonable to assume that unavoidable urge incontinence that appears suddenly is more distressing than an avoidable symptom such as stress incontinence. The avoidability of this symptom could be one explanation for the results of another study by our group [15], which shows that ‘high-severity’ stress incontinence causes moderate/much distress among a much higher proportion of affected men (67%) than in men with a ‘low-severity’ level of the symptom (21%). Thus, when it occurs, it causes high levels of distress, but because it is avoidable, the affected person avoids risky situations and thereby prevents negative effects on QoL.

Although ‘other’ incontinence was not the most prevalent LUTS, it had a considerable effect on self-assessed health, sadness and happiness. It is therefore important to assess not only highly prevalent LUTS but also symptoms with a low prevalence and which affect QoL in the clinical situation. The findings by Peters et al. [16], that nocturia influences ‘everyday life’, supports the present finding that this symptom has negative effects on perceived health, sadness and happiness. ‘Weak stream’ was also significantly correlated with a lower level of self-assessed health and happiness, and to a higher level of sadness. This has also been discussed previously [17], and could reflect fear of prostate cancer.

The differences between men with LUTS and men with no LUTS with respect to social status, education, marital status, smoking, physical activity and UTI indicate that LUTS have a particular impact on self-assessed health and happiness. Koskimäki et al. [5] found that the RR of a reduction in QoL after adjusting for age and different diseases was higher in men with LUTS than in with men with no LUTS. Unfortunately, in the present study, no specific questions were asked about other diseases.

LUTS were self-reported and the classification based on a questionnaire answered in the home environment. No clinical investigations were undertaken to validate the reported LUTS. The use of a questionnaire in the home environment probably results in fewer investigator errors than, for example, a personal interview [18,19]. As a result, the misclassifications that might have occurred using this method are difficult to assess objectively, but the risk should be low, as the DAN-PSS is a validated questionnaire designed for self-assessment [20]. The Swedish population register provides information on all residents in the country, the present study is based on a large population, and we see no indications that men in this community differed from men in the rest of the country. It is always risky to generalize results from one study population to others, but the prevalence of LUTS is commonly described as being about the same in other countries of the world.

It is difficult to define when symptoms do not merely constitute a normal physical condition or behaviour; LUTS should be evaluated individually, together with the patient’s discomfort level from the same symptom. In the present study, we included all LUTS, irrespective of discomfort level, and included the symptom if it was reported at any level in the DAN-PSS. For some LUTS the reported symptom level might represent a ‘normal’ condition, rather than a pathological condition for that individual. Counting these low-grade symptoms together with high-grade symptoms might dilute the results obtained. Self-assessments of LUTS have previously shown limitations; Malmsten et al. [21] found that self-reported urinary incontinence could not be verified objectively in 4.6% of the participants. In the present study, self-assessed health, sadness and happiness were evaluated by three questions from a disease-independent questionnaire, the SF-36; we consider that the most reliable evaluation of LUTS, as well as quality factors, is the self-assessment of specific questions and not a summarized score from many different questions.

Bias could have been introduced during the selection of the study base (Fig. 1). The cohort in the present study consisted of 1008 men, i.e. 504 who 12 months earlier reported the occurrence of one or more of three LUTS [1], and 504 age-matched men from the same community. To minimize misrepresentation, two postal reminders were sent to those not

<table>
<thead>
<tr>
<th>Table 6 The prevalence of tested scores, as n/N (%) and RR (95% CI) in men with different numbers of reported LUTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of symptoms</strong></td>
</tr>
<tr>
<td><strong>Group</strong></td>
</tr>
<tr>
<td>Low score for health</td>
</tr>
<tr>
<td>RR</td>
</tr>
<tr>
<td>High score for sadness</td>
</tr>
<tr>
<td>RR</td>
</tr>
<tr>
<td>High score for happiness</td>
</tr>
<tr>
<td>RR</td>
</tr>
</tbody>
</table>
responding, but more men who had reported LUTS answered the questionnaire than men with no earlier reported LUTS. Consequently, nothing indicates that the differences between men with LUTS and the controls are large enough to jeopardise the study results, but we cannot exclude the possibility that the 26% who did not respond biased the results. Even if the present results confirmed the need to focus on the reasons for health-care seeking, which have been poorly documented and analysed.

CONFLICT OF INTEREST

None declared.

REFERENCES

18 Steineck G, Ahlbom A. A definition of bias founded on the concept of the study base. Epidemiology 1992; 3: 477–82

Correspondence: Gabriella Engström, Department of Caring Sciences and Public Health, Mälardalen University, Box325, SE-63105 Eskilstuna, Sweden.
e-mail: gabriella.engstrom@mdh.se

Abbreviations: DAN–PSS, Danish Prostatic Symptom Score; SF–36, Medical Outcomes Study Short-Form 36 health survey; RR, relative risk.

APPENDIX 1

In general, would you say your health is?
   a) Excellent; b) Very good; c) Good; d) Moderate; e) Bad

Have you felt sadness?
   a) All of the time; b) Most of the time; c) Some of the time; d) Part of the time; e) A little of the time; f) None of the time

Have you been happy?
   a) All of the time; b) Most of the time; c) Some of the time; d) Part of the time; e) A little of the time; f) None of the time
Nocturia in relation to somatic health, mental health and pain in adult men and women

RAGNAR ASPLUND, SVEN-UNO MARNEFOFT*, JOHN SELANDER* and BENGT ÅKERSTRÖM†

Family Medicine Stockholm, Karolinska Institute, Huddinge, *Department of Public Health, Division of Rehabilitation Medicine, Karolinska Institute, Stockholm, and Centre for Studies on National Social Insurance, †Department of Nursing and Health Sciences, Mid Sweden University, Östersund, Sweden

Accepted for publication 12 November 2004

OBJECTIVE

To assess the relationship of nocturia to somatic health, mental health and bodily pain.

SUBJECTS AND METHODS

A randomly selected group of men and women aged 20–64 years, living in three small municipalities in northern Sweden, or in the city of Östersund or in Stockholm, were sent a postal questionnaire containing questions on somatic and mental health, satisfaction with life, pain, nocturnal voiding, work and sick-listing from work.

RESULTS

Reports (from 1948 respondents) on poor somatic and mental health and on pain all increased in parallel with increasing frequency of nocturnal micturition. In a multiple logistic regression analysis with sex, age, somatic health, mental health and bodily pain as the independent variables, significant independent correlates (odds ratios, confidence intervals) of nocturnal micturition (two or more episodes vs none or one) were: age 45–59 vs 20–44 years, 1.9 (1.3–2.7), ≥60 vs 20–44 years, 3.8 (2.4–6.0); somatic health, poor vs good, 2.3 (1.4–3.7); mental health, poor vs good, 1.9 (1.2–3.0); pain, rather mild vs very mild or none, 1.5 (1.0–2.3); rather severe vs very mild or none, 1.9 (1.1–3.2); and very severe vs very mild or none, 6.0 (2.5–14.0). Gender was deleted by the logistic model. Sick-leave for ≥60 days during the past year was reported by 4.9%, 10.6%, 5.6% and 38.9% of the men with none, one, two or ≥3 nocturnal voids, respectively, and by 10%, 12.4%, 23% and 46.7% (both P < 0.001) of the corresponding women, respectively. Life satisfaction decreased in parallel with increased nocturia.

CONCLUSION

The impairment of both somatic and mental health was associated with increased nocturnal voiding. Pain was associated with a substantial increase in nocturia after adjusting for age and somatic and mental health. Sick-leave was more common in association with more nocturnal voids.

KEYWORDS

mental health, nocturia, somatic health, pain

INTRODUCTION

Nocturia is a common complaint in adults, especially in elderly people, and both health and quality of life are often impaired in those with nocturia [1–3]. Somatic disorders such as cardiac diseases, poorly controlled diabetes, sleep apnoea syndrome and chronic pelvic pain are associated with nocturia [4–6]. Sleep complaints and different nocturnal symptoms, e.g. muscle cramp in the legs and leg tingling, are also reported to be increased in parallel with more nocturnal voids [1]. In addition, nocturia is also associated with different kinds of medication, e.g. diuretics and analgesics [4].

The aim of the present study was to analyse the relationship between somatic and mental health as one factor and nocturnal voids as the other, and to investigate the possible relationship between nocturnal voiding and bodily pain in a group of adult men and women.

SUBJECTS AND METHODS

A postal questionnaire with an explanatory letter was sent to 3000 men and women aged 20–64 years living in different areas of Sweden and randomly selected from the National Population Register on 1 November 2003. The selected people were distributed by residence as follows: 500 from each of the three small, sparsely populated municipalities in northern Sweden (Härjedalen, Strömsund and Åre) with populations of 11 059, 13 293 and 9635, respectively; 500 from the city of Östersund (population 58 342); and 1000 from Stockholm, the capital of Sweden, with a population of 761 949 (one of the 18 municipalities of the county of Stockholm).

Those who had not replied within 2 weeks were sent a reminder, those who had not replied after 2 further weeks received a second reminder with another copy of the questionnaire, and those who had not replied 2 weeks after this reminder received a final reminder after another 2 weeks.

The questionnaire contained questions on age and sex, somatic and mental health, sleep, bodily pain and the number of nocturnal voids (Appendix); the question on nocturnal voids analysed in this study referred to the last few days. The question on nocturia has been used extensively in our questionnaire surveys for exploring nocturia in relation to different diseases and symptoms since the first report was published in 1992 [1]. The number of voids recorded during three consecutive nights by a large group of men and women showed acceptable day-to-day variability [1,7].

There were also questions about attitudes to health and disease, sick-listing from work, relations with the family, relatives and friends, and work and unemployment. The subject’s somatic health was considered to be good if the response in the questionnaire was ‘Very
In a multiple logistic regression analysis with bodily pain as the independent variables, significant independent correlates, as odds ratios (95% CI) of nocturnal voids [two or more vs none or one] were: age 45–59 vs 20–44 years, 1.9 (1.3–2.7); ≥60 vs 20–44 years, 3.8 (2.4–6.0); somatic health, poor vs good, 2.3 (1.4–3.7); mental health, poor vs good, 1.9 (1.2–3.0); pain, rather mild vs very mild or none, 1.5 (1.0–2.3); rather severe vs very mild or none, 1.9 (1.1–3.2); very severe vs very mild or none, 6.0 (2.5–14.0). Sex was deleted by the logistic model. The Hosmer-Lemeshow goodness-of-fit test for the final model yielded a chi-square of 8.5 on eight degrees of freedom (P = 0.553).

The statement 'I am on the whole satisfied with my life' was answered 'I totally agree' by 53.4% of the men with no nocturnal voids and by 46.8%, 32.2% and 11.1% of the men with one, two, and three or more, respectively (P < 0.001); among the women the corresponding frequencies were 57.9%, 50.9%, 39.5% and 18.2% (P < 0.001).

Sick-listing for ≥7 days during the past year was reported by 13.4% of the men with no nocturnal voids and by 19.9%, 20.4% and 55.6% of the men with one, two, and three or more, respectively (P < 0.001); among the women the corresponding frequencies were 24.7%, 25.4%, 44.4% and 50% (P < 0.001). Correspondingly, sick-listing for ≥60 days during the recent year was reported by 4.9%, 10.6%, 5.6% and 38.9% of the men, and 10%, 12.4%, 23.0% and 46.7% (both P < 0.001) of the women, respectively.

### DISCUSSION

In the present study, which comprised randomly selected men and women aged 20–64 years, more nocturnal voids were associated with an impairment of both somatic and mental health, and these two aspects of health impairment were increased proportionally with nocturnal voiding frequency (Fig. 1a). In previous studies, elderly people with nocturia have impaired general health, as well as sleep deterioration, many sleep-disturbing somatic symptoms, daytime sleepiness and a poor quality of life, and have a lower life-expectancy [1,8].

The present multiple regression analysis showed that the interrelationships of somatic and mental health with nocturia were independent of each other and of age. Nocturnal urinary frequency is often associated with somatic diseases, or with an age-related increase in nocturnal urine output or a reduced bladder capacity, or a combination of these two conditions [9,10]. The use of the term 'nocturia' in the present study requires clarification; in the standardized urological terminology, nocturia is defined as '...the complaint that the individual has to wake at night one or more times to void' [11]. Among the present subjects several were probably awake at night as a consequence of different sleep-disturbing symptoms, e.g. musculo-skeletal pain, nightmares, sleep apnoea or menopausal sweating, and thus some nocturnal voids might not have met the above-mentioned criterion. However, in a questionnaire survey among 1115 men and women (39.5% men), in those who reported three or more nocturnal voids, the reported numbers of nocturnal awakenings were 3.4 and 3.5 in men and women, respectively, and there was also reasonably good conformity between few awakenings and fewer voids than three per night [7]. Almost all nocturnal voids in the present age group can be presumed to be associated with waking and getting out of bed. This supports the conclusion that most awakenings at night occur in association with voiding, i.e. that the standardized definition of nocturia was met for most nocturnal voids.

The possible cause-effect relationship between poor mental health and nocturia should be considered. In a study among men with LUTS from prostatic obstruction, these symptoms occurred in association with emotional ill-health [12]. In a recent study, major depression was associated with a six-fold increase in the occurrence of two or more nocturnal voids.
nocturnal voids in men, and a three-fold increase in such episodes in women, after age and health had been taken into account [13]. This relationship might to some extent be explained in that there is a close relationship between nocturia and sleep impairment, and that sleep impairment is always present in major depression, as it is one of the diagnostic criteria of such depression [14].

Satisfaction with life on the whole was much less frequent in those who were troubled by nocturnal voids. In a previous study in women aged 40–64 years, more nocturnal voids were associated with more unfavourable reports on happiness, confidence in the future and appetite [15].

One surprising finding in the present study was that pain in general was still associated with a substantial increase in nocturnal voids, after adjusting for age and somatic and mental health (Fig. 1b). Other connections between nocturia and painful conditions have also been reported in elderly people, e.g. nocturnal muscle cramps in the legs and spasmodic chest pain [1]. Nocturia is also increased in women with chronic pelvic pain [6]. Koskimäki et al. [16] reported a 70% increase in LUTS and a 30% increase in nocturia among men aged 50–70 years with arthritis. The authors concluded that arthritis affects both the storage and emptying of the bladder.

The relationship between bodily pain and nocturia might be explained in that some analgesics influence renal function. Prostaglandin-inhibiting analgesics reduce urine output by a specific effect on the kidney, and they enhance the propensity for fluid retention, which can increase urine output at night, when the effect of the analgesic compound has subsided [17]. Another possible reason for the increase in nocturia in association with the use of analgesics is that analgesic use serves as a proxy for pain.

The increase in nocturnal voids in subjects with bodily pain may also reflect the increased propensity for sleep impairment in such people. This interpretation is supported by findings in a study of elderly men and women (mean age 73 years, SD 6), among whom poor sleep was shown to be 2.7 (1.7–4.3) times and 4.8 (3.5–6.4) times more common, respectively, in those who were very often troubled by musculo-skeletal pain than in those who very seldom or never experienced such pain [18].

Sick-listing was greater in both men and women with more nocturnal voids, and there was a proportional increase in the prevalence of absence for sickness both in the group with ≥7 days absent per year and in the group with ≥60 days absent per year. Such a relationship was previously reported in Swedish women.

FIG. 1. A, The frequency (%) of poor somatic health in men and women, and of poor mental health in men and women (all P < 0.001), in relation to the number of nocturnal voids. B, The distribution of different numbers of nocturnal voids (%) in men and women with no or very mild pain (1), rather mild pain (2), rather severe pain (3) and very severe pain (4) (P < 0.001 both for men and women). In both plots the number of voids (none, one, two, three or more) are represented by the white, light red, green and red bars, respectively.
aged 40–64 years, among whom the duration of sick-leave was 15 days per year in the group with none and 75 days per year in those with three or more nocturnal voids. Women who voided three or more times per night also consulted a doctor twice as often as those with no nocturnal voids, and were treated with drugs 2.5 times as often [15]. In a study of productivity, vitality and utility in a group of healthy professionally active individuals with nocturia (mean age 52.9 years, 50% of men), compared with a randomly selected control group, Kebel et al. [19] found that sick-leave for any reason was reported almost twice as often in the nocturia group. The productivity and overall work impairment was also lower in this group.

In the present study the distribution of nocturnal voids was similar in men and women (Table 1), which is in line with previous findings [1,20]. The relation between somatic health and mental health as one factor and nocturnal voiding as another showed no gender differences (Fig. 1a).

In conclusion, among randomly selected men and women aged 20–64 years, nocturnal voiding was associated with impairment of both somatic and mental health. Pain was associated with a substantial increase in nocturnal voids after adjusting for age and for somatic and mental health. Satisfaction with life was lower and sick-leave more common in those with nocturnal voids after adjusting for age and for

ACKNOWLEDGEMENTS

This study was supported by the Social Insurance Office and its co-operative partners in the project ‘Early and Co-ordinated rehabilitation’ in the county of Jämtland, Sweden.

CONFLICT OF INTEREST

None declared. Source of funding: Jämtland County Council.

REFERENCES

8 Asplund R. Mortality in the elderly in relation to nocturnal micturition. BJU Int 1999; 84: 297–301
15 Asplund R, Åberg H. Nocturnal micturition, sleep and well-being in women of ages 40–64 years. Maturitas 1996; 24: 73–81
19 Kobelt G, Borgström F, Mattiasson A. Productivity, vitality and utility in a group of healthy professionally active individuals with nocturia. BJU Int 2003; 91: 190–5

Correspondence: Ragnar Asplund, Tallvägen 3, S-833 34 Strömsund, Sweden.

© 2005 BJU INTERNATIONAL

APPENDIX

Statements in the questionnaire that were analysed (original in Swedish).

Sex: man/woman

Age (years): 20–29 / 30–44 / 45–59 / ≥60

My somatic health is:

Very good / Rather good / Rather poor / Very poor

My mental health is:

Very good / Rather good / Rather poor / Very poor

I get up . . . times per night for micturition.

Bodily pain

None or very mild / Rather mild / Rather severe / Very severe

Sick-listing during the past year (days):

0–6 / 7–29 / 30–59 / 60–179 / ≥180

I am on the whole satisfied with my life:

Agree totally / Agree partly / Disagree partly / Disagree totally.
Nocturia, depression and antidepressant medication

RAGNAR ASPLUND*, SUSANNE JOHANSSON†, SVANTE HENRIKSSON‡ and GÖRAN ISACSSON+

*Family Medicine Stockholm, and †Neurotec, Division of Psychiatry, Huddinge University Hospital, Karolinska Institute, Huddinge, Sweden and ‡The Research and Development Unit, Jämtland County Council, Östersund, Sweden

Accepted for publication 1 December 2004

OBJECTIVE

To assess the possible relationship between treatment with selective serotonin-reuptake inhibitors (SSRIs) and the occurrence of nocturia.

RESULTS

The questionnaire was completed by 1375 subjects, of whom 609 (44%) were men; the response rate was 69%. Prescription data were available for all respondents. The mean (SD) age of the men and women participating were 48.0 (18.2) and 50.1 (19.1) years, respectively. Two or more nocturnal micturition episodes were reported in 15.6% of the men and 16.5% of the women. In a multiple logistic regression analysis, independent correlates for two or more nocturnal voids vs no more than one were: age 45–59 years vs <45 (odds ratio 2.9; 95% confidence interval 1.9–4.7); age 60–74 vs <45 (6.0; 3.7–9.8); age > 75 vs <45 (13.4; 7.9–22.6); major depression, yes vs no (4.6; 2.8–7.5); and being on treatment with SSRI, yes vs no (2.2; 1.1–4.5). Gender was deleted by the logistic regression model.

CONCLUSION

Major depression has previously been found to be associated with increased nocturnal micturition. In the present study, twice as many men and women treated with SSRIs as those not so treated had two or more nocturnal voids, after adjusting for major depression and age. The implication for the risk of fall injuries is discussed.

KEYWORDS

antidepressants, major depression, nocturia, selective serotonin-reuptake inhibitors, SSRI

INTRODUCTION

Nocturia is a common complaint in adult and elderly people; its prevalence increases in parallel with increasing age and has a profound influence on the death rate, health and quality of life [1,2]. Nocturia is caused by an increase in the nocturnal urine output, an impaired bladder capacity or a combination of these two mechanisms [3].

In a previous study we found that major depression (MD) was associated with a six-fold increase in nocturia in men and a three-fold increase in women, after age and health had been taken into account [4]. Possible pathogenetic mechanisms of this relationship may involve both increased nocturnal diuresis resulting from a disturbed 24-h rhythm of vasopressin secretion, and a decreased nocturnal bladder capacity caused by a central and/or peripheral serotonergic effect [5–8]. Both a bladder contraction and simultaneous relaxation of the urethra are necessary for emptying the bladder [8,9]. In the pontine micturition centre in the brain, it is proposed that impulses indicating urgency from the urogenital tract are integrated with signals from the cortex and hypothalamus that determine whether micturition is socially and environmentally appropriate [9].

Many people with depression are treated with antidepressants and there are reports that some antidepressants are associated with an increased risk of incontinence [10], and that one antidepressant drug, duloxetine, is used successfully in the treatment of this condition [11]. The aim of the present study was to investigate whether the previously observed increase in nocturia in men and women with depression could be attributed to the depression per se, to antidepressant medication or to both mechanisms.

SUBJECTS AND METHODS

All men and women aged ≥18 years, born on one of two defined days each month of the year and resident in any of three defined parishes in the city of Östersund, Sweden, were sent a postal questionnaire with an explanatory letter. Those who had not replied within 2 weeks were sent a reminder by postcard, and those who had not replied after 2 further weeks received a second reminder with a new copy of the questionnaire.

The answers to the questions on depression, sleep and nocturia were analysed. To obtain data on nocturnal micturition, the question ‘I usually get up . . . times for micturition per night’ was included [1]. For depression diagnostics, the Major Depression Inventory (MDI) was used [12]. The MDI contains all nine symptoms of a DSM IV major depression episode [13]. The procedure for analysing data from the MDI was described in detail previously [4].

Prescription data on antidepressant drugs were extracted from a register in the county of Jämtland, Sweden, in which all drug prescriptions from 1970 onwards for all inhabitants with one of four defined birthdays in all months of the year are recorded. Prescriptions issued 1 year before the distribution of the questionnaire and as long as data were available (mean 6 months,
Prescription data were available for all those responding or not.

The mean (so) ages of the men and women participating were 48.0 (18.2) and 50.1 (19.1) years, respectively; the proportion of elderly participants (>75 years old) was somewhat larger in the women than in the men: (P < 0.05) (Table 1).

In all 609 men SSRIs had been used for <3 months before completing the questionnaire by three (0.5%), for 3–6 months by four (0.6%) and for >6 months by 18 (2.9%); the corresponding values in the 766 women were four (0.5%), seven (0.9%) and 43 (5.6%) (P < 0.05). After the questionnaire had been completed, 17 (2.8%) of the men and 45 (5.9%) of the women received one or more SSRI prescriptions (P < 0.01). There was no significant difference in the prescription pattern between those who had answered the questionnaire and those who had not.

Four (13.7%) of the 29 men with MD and 11 (22.9%) of the 48 women with MD were taking an SSRI. Of the 16 men on SSRIs four had MD and of the 565 men not on an SSRI four (0.7%) had MD (P < 0.05). The corresponding values for women were 11 of 32 (34%) and 52 of 714 (7.3%) (P < 0.001). Treatment with an SSRI was 5.4 (1.5–19.7) times more common in men and 3.6 (1.5–8.6) times more common in women with two or more nocturnal micturition episodes than in those with no such episodes.

In the multiple logistic regression analysis independent correlates for two or more nocturnal voids vs no more than one episode were: age 45–59 vs <45 years, 2.9 (1.9–4.7); age 60–74 vs <45, 6.0 (3.7–9.8); age >75 vs <45, 13.4 (7.9–22.6); MD, yes vs no, 4.6 (2.8–7.5); and taking an SSRI, yes vs no, 2.2 (1.1–4.5). Gender was deleted by the logistic regression model. The Hosmer-Lemeshow goodness-of-fit test for the final model yielded a chi-square of 1.69 on five degrees of freedom (P = 0.89).

### DISCUSSION

The main finding in the present study was that treatment with an SSRI was associated with greater nocturia, after MD and age had been taken into account. We found no previous report dealing with the possible relationship between nocturia and SSRI. The result must be interpreted with some caution, as there were relatively few subjects taking SSRIs, but the good conformity with SSRI prescription data between those responding or not supports the conclusion that the prescription information was representative for the population in the investigated geographical area.

There were no questions on somatic diseases or on symptoms with a possible influence on nocturia, e.g. heart diseases, sleep apnoea or BPH, although depression can be expected to be more common in association with such diseases [15–18]. Nor did we analyse the possible influence of habits such as alcohol intake, smoking or the intake of coffee or tea, although such habits are associated with changes in nocturia and may differ in people with or with no depression [19]. However, we do not think that these factors can explain more than a minor part of the relationship between nocturia and SSRI use.

The analysis was restricted to SSRIs, as this class of antidepressants has been the predominant one in the county of Jämtland since 1995 [20]. However, a favourable feature with reference to the aim of the study was that in addition to people with MD treated with an SSRI, the study group included both those with untreated MD and those using an SSRI who did not meet the criteria for MD. This improved the possibility of analysing the relationship between nocturia and SSRIs independently of MD.

Most subjects with MD were not being treated with an SSRI. Other studies have similarly shown that most depressed people in Sweden are medically untreated or only sporadically treated [20,21]. Most of those who were treated with an SSRI had been on their medication for >6 months. The dose of SSRI was in almost all cases in accordance with current Swedish recommendations for treating MD. This suggests that those who were on an SSRI but did not meet the criteria for MD were in remission.

Previous reports on urinary symptoms in association with SSRIs are contradictory. In a retrospective follow-up study among 450 000 residents living in eight Dutch cities, Movig et al. [10] identified 13 531 first-time users of an SSRI between 1994 and 1998. They found a 61% increase in the relative risk for urinary incontinence caused by the SSRI and also that

### RESULTS

The questionnaire was initially completed by 860 people and after reminders, a further 515 answers were received. Thus there were 1375 evaluable questionnaires, of which 609 (44%) were from men. Among recipients who could be expected to answer (1971 in all), the response rate was 69%.

### TABLE 1 The distribution (n,%) of major depression among men and women of different age groups

<table>
<thead>
<tr>
<th>Age, years</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>20–29</td>
<td>0</td>
<td>14 (8.8)</td>
</tr>
<tr>
<td>30–44</td>
<td>10 (7.4)</td>
<td>14 (9.9)</td>
</tr>
<tr>
<td>45–59</td>
<td>10 (5.6)</td>
<td>9 (4.1)</td>
</tr>
<tr>
<td>60–74</td>
<td>7 (6.1)</td>
<td>5 (3.3)</td>
</tr>
<tr>
<td>&gt;75</td>
<td>2 (3.8)</td>
<td>6 (6.6)</td>
</tr>
<tr>
<td>Total</td>
<td>29 (4.8)</td>
<td>48 (6.3)</td>
</tr>
</tbody>
</table>

### NOCTURIA, DEPRESSION AND SSRI

The analysis was used, with the Hosmer–Lemeshow goodness-of-fit test for assessing goodness-of-fit.
sertraline was associated with the highest risk. In contrast, an antidepressant that influences both the serotonin and the noradrenaline pathways of the CNS, duloxetine, has been found to reduce incontinence [11,22]. These divergent results may reflect differences in action of the different antidepressants.

MD is a prevalent condition; in a Swedish study it was found that up to 70 years old, the cumulative probability of suffering a first episode of depression was 27% in men and 45% in women [23]. Many authors have called attention to the widespread under-diagnosis and under-treatment of MD [24,25]. The most important reason for recognition and adequate treatment of this condition is that it causes much suffering and disability, and that it can be effectively treated [22]. It may therefore be expected that antidepressant treatment will become more common in the future [26].

Nocturia is an important risk factor for falls and particularly for hip fractures, with serious consequences in older people. Mortality after a hip fracture is high: a third of patients die within a year after the accident [27]. There is also greater depression among elderly people with hip fracture, and the depression can both be a cause and a consequence of the accident [28,29]. In the present study the occurrence of two or more nocturnal voids was reported twice as often by men and women on an SSRI than by those without such medication, after adjusting for age and MD. The results may indicate that elderly people on an SSRI may run an especially high risk of fall injuries. The design of the study did not allow a comparison between those on different types of SSRI for the occurrence of nocturia. This would be an important topic for further studies. A greater risk of hip fractures was previously reported among antidepressant users, and SSRI and tricyclic antidepressants are associated with an increase of similar magnitude [30].

In summary, previous studies have shown that MD is associated with an increase in nocturnal micturition. In the present study, twice as many men and women treated with SSRIs had two or more nocturnal voids than had those without such treatment, after MD and age had been taken into account. The results need to be confirmed in a larger study where nocturia in people using different kinds of SSRI can be analysed.

CONFLICT OF INTEREST

None declared.

REFERENCES

24 Davidson JR, Meltzer-Brody SE. The underrecognition and undertreatment of depression: what is the breadth and depth of the problem? J Clin Psychiatry 1999; 60 (Suppl. 7): 4–11

Correspondence: Ragnar Asplund, Tallvägen 3, S-833 34 Strömsund, Sweden.
e-mail: rasplund@telia.com or ragnar.asplund@jll.se

Abbreviations: (MD), (Major Depression) Inventory; SSRI, selective serotonin-reuptake inhibitor; OR, odds ratio.
Combined external urethral bulking and artificial urinary sphincter for urethral atrophy and stress urinary incontinence

NADEEM U. RAHMAN, THOMAS X. MINOR, DONNA DENG and TOM F. LUE
Department of Urology, University of California, San Francisco, USA
Accepted for publication 1 November 2004

OBJECTIVE
To describe a technique of externally bulking the urethra with a soft-tissue graft before placing another artificial urinary sphincter (AUS), as when placing another AUS for recurrent male stress urinary incontinence (SUI) other manoeuvres, e.g. placing a tandem cuff or transcorporal cuff, must be used to obtain urinary continence in an atrophic urethra, and each is associated with morbidity.

PATIENTS AND METHODS
From January 2003 to July 2004, five patients (mean age 74 years, range 62–84) treated by radical prostatectomy were referred for recurrent SUI after placing an AUS (four, including one with urethral erosion) or a male sling (one, with a resulting atrophic urethra). Each patient was treated with an external urethral bulking agent (Surgisis® ES, Cook Urological, Spencer, Indiana) and had an AUS placed.

RESULTS
In each patient the greatest urethral circumference was <4 cm. To place a functional 4 cm cuff, the diameter of the urethra was enhanced by wrapping it with Surgisis ES. Continence was significantly improved in all patients except one 84-year-old man who had the replanted artificial sphincter removed because of erosion 14 months after surgery.

CONCLUSION
In cases of severe recurrent SUI from urethral atrophy after placing an AUS, externally bulking the urethra with Surgisis ES before placing another AUS is well tolerated, and gives satisfactory results.

KEYWORDS
urethral atrophy, artificial urinary sphincter, stress urinary incontinence

INTRODUCTION
The use of the AMS 800 (American Medical Systems, Minnetonka, Minnesota) artificial urinary sphincter (AUS) for male stress urinary incontinence (SUI) after radical prostatectomy was first popularized in 1972, and has now become the ‘gold standard’ treatment, with patients reporting a >90% improvement in quality of life afterward [1]. The absolute continence rate after an AUS is 73–90% [2–4], but with time some patients have recurrent incontinence, generally attributed to urethral atrophy beneath the cuff. Many surgical options have been described to treat such a condition, including surgically reducing the cuff size, placing a second tandem AUS cuff, and recently, a transcorporal cuff implantation [5–7]. Each of these methods is associated with some potential complications and deficiencies.

Herein we describe a simplified treatment for severe SUI after an AUS secondary to urethral atrophy, using a sterilized natural biomaterial as an external urethral bulking agent, followed by placing another AUS.

PATIENTS AND METHODS
From January 2003 to April 2004, five patients (mean age 74 years, range 62–84) with recurrent SUI after AUS or a male sling operation were treated with external bulking using Surgisis® ES (Cook Urological, Spencer, Indiana) followed by placing an AUS. After prostatectomy at an outside institution, four patients had an AUS placed 3–10 years earlier to treat SUI. All had a 4-cm cuff placed at the time of their first incontinence operation. Each patient was subsequently referred for the management of recurrent SUI requiring more than five pads daily; an evaluation determined that each had developed urethral atrophy. Notably, one patient had urethral erosion requiring earlier AUS removal. The fifth patient developed an atrophic urethra after a male sling was placed following prostatectomy. These five patients with recurrent SUI and urethral atrophy were treated with external bulking using four-ply Surgisis ES derived from porcine small intestinal submucosa, followed by placing an AUS.

The defect was repaired with the patient under general or spinal anaesthesia, with intravenous antibiotics given before inducing anaesthesia. After sterile genital preparation, we used either a perineal vertical incision over the bulbar urethra, with the patient in a high lithotomy position, or a transverse incision at the penoscrotal junction with the patient in a supine ‘frog-leg’ position. In the three patients with a sphincter cuff in place, the corpus spongiosum was exposed and the AUS activated via the scrotum to monitor the inflation/deflation cuff mechanism. This confirmed the cause of the SUI to be urethral atrophy and not mechanical cuff malfunction. A pseudocapsule was generally noted around the cuff, requiring careful dissection to free the device from the corpus spongiosum. After removing the cuff and remaining hardware, the urethral circumference was measured. Before bulbar urethral isolation in the
remaining two patients (one had previous cuff erosion and the other a failed male sling operation), urethroscopy was used to exclude stricture disease. In all five patients the urethral circumference was <4 cm (2.5–3.5 cm). To provide external bulking, a rectangular piece of Surgisis ES with a width equal to that of the sphincter cuff was positioned around both the urethra and Surgisis ES [Fig. 1]. Tubing for the reservoir and pump were connected in the standard fashion. The system was tested and deactivated. A 12 F urethral catheter was placed overnight. The device was activated 6 weeks later.

RESULTS

At a mean (range) follow-up of 11 (4–14) months, all patients reported a significant improvement in their continence and quality of life. Two patients are completely dry, with no pad usage; two had minimal SUI, requiring no or one pad per day. One patient continues to require one or two pads per day for protection, probably because of his urodraulically confirmed small bladder capacity. This patient had no leakage during cough, sneeze or Valsalva manoeuvre in the office setting. There were no complications after surgery (Table 1). After submission of the manuscript, Patient 3, an 84-year-old man with severe pulmonary disease, had the replanted artificial sphincter removed because of erosion 14 months after surgery.

DISCUSSION

The AUS is considered to be the ‘gold standard’ for treating severe UI, with patient satisfaction ratings of up to 90%. However, over time, incontinence seems to worsen, with the most common mechanism being urethral atrophy under the cuff, causing a decrease in coaptation of the cuff. If the current cuff size is 4 cm, reducing it is not a viable option as this is the smallest available size. In this situation, other measures must be taken. Brito et al. [5] described placing a second distal AUS cuff in tandem with a more proximal first (original) cuff for this situation, with a success rate of up to 90%, but the risk of ultimately developing urethral atrophy remains. Future revision will be more difficult because the corpus spongiosum in the more distal portion is even smaller in diameter. Transcorporal placement of either a second tandem cuff or first cuff has also been reported; this technique was also very successful but is more demanding and associated with the potential risk of erectile dysfunction [6].

The use of extracellular matrix as a scaffold for tissue reconstruction has been investigated extensively in the lower urinary tract [8]. Sources have included small intestine submucosa and the urinary bladder itself. Work using animal models [9–12] of urethral, ureteric, bladder wall and vaginal replacement have resulted in the present use of these materials in humans, with a high success rate. These studies showed that the matrix serves as a temporary, rapidly degraded scaffold that is replaced by organized and functional smooth muscle and urothelium [8–19]. The rate of resorption of the scaffold has been surprisingly rapid, with as much as 90% of the scaffold replaced within 28 days [11,13,18]. These results indicate that the host cellular infiltrate is rapid, diffuse and different from the typical fibroblastic ingrowth seen with tissue injury or purified collagen scaffold materials.

If the same resorption rate were similar in humans it would be expected that the Surgisis around the corpus spongiosum would be replaced by host tissue within 3 months. That none of the present five patients had recurrent urinary leakage after a follow up of 4–14 months is certainly encouraging. While these results remain preliminary, the technique has certain advantages. Placing an external artificial graft around the urethra may be protective and delay the onset of further urethral atrophy. This technique also requires no additional dissection or manipulation of the corpus spongiosum or corpora cavernosa. A longer follow-up will be needed to determine if there is protection against urethral atrophy in the long term. Studies are also needed to examine whether other grafting materials are suitable for the same purpose.
In conclusion, severe recurrent male SUI after placing an AUS can be adequately managed with external urethral bulking with Surgisis ES and a repeat AUS, with minimal morbidity.

CONFLICT OF INTEREST
None declared.

REFERENCES
12 Yoo JJ, Meng J, Oberpenning F, Atala A. Bladder augmentation using allogenic bladder submucosa seeded with cells. Urology 1998; 51: 221–5

Correspondence: Tom F. Lue, University of California, San Francisco, 400 Parnassus Avenue, Box 0738, San Francisco, CA 94143, USA.
E-mail: tlue@urol.ucsf.edu

Abbreviations: SUI, stress urinary incontinence; AUS, artificial urinary sphincter.
Day-case sling surgery for stress urinary incontinence: feasibility and safety

SUBHASIS K. GIRI, JOHN DRUMM, JEAN A. SAUNDERS*, JANE MCDONALD and HUGH D. FLOOD
Department of Urology, Mid-Western Regional Hospital and National Institute of Health Sciences, and *Statistical Consulting Unit, University of Limerick, Ireland
Accepted for publication 29 November 2004

OBJECTIVE
To prospectively assess the feasibility for discharge 10 h after a porcine dermal pubovaginal sling procedure (PVS), to examine the surgical factors (postoperative complications) affecting discharge, and to measure the short-term cure rate for stress urinary incontinence (SUI).

PATIENTS AND METHODS
Between June 2003 and December 2003, 40 consecutive patients with SUI and scheduled for treatment using a porcine dermal sling were enrolled in this prospective study. Patients were admitted with a planned overnight stay and returned to the ward with no urinary catheter. Outcome measures were bladder emptying efficiency (EE) at 10 h after surgery, time intervals to the first three spontaneous voids, EE of the first three voids, time required to achieve an EE of ≥75%, a visual analogue scale pain score, perioperative complications, and short-term cure rate of SUI. Patients were considered suitable for discharge from hospital when the EE was ≥75% or when they were self-catheterizing confidently with adequate pain control and no significant complication. All patients were followed for 6 months.

RESULTS
The median EE at 10 h was 61%; 16 patients (40%) achieved efficient emptying and were suitable for discharge 10 h after surgery. The median intervals to the first three spontaneous voids were 7, 10 and 17 h, and the median EEs for the first three voids 46%, 61% and 75%. The median visual analogue scale pain score was 3.5. Patients with intrinsic sphincter deficiency (ISD) were significantly less likely to achieve efficient emptying at 10 h (39% vs 70%). Overall SUI was cured or improved in 90% of patients at the 6-month follow-up.

CONCLUSIONS
In the present study only 40% of patients were suitable for day-case sling surgery. Early bladder emptying inefficiency was the main limiting factor. Exclusion of patients with ISD and possibly decreasing the EE threshold to 50% would improve the discharge rate. The short-term results of this PVS are similar to those obtained with the autologous fascial sling.

KEYWORDS
stress urinary incontinence, minimally invasive surgery, day-case surgery, pubovaginal sling

INTRODUCTION
Stress urinary incontinence (SUI) is a common problem [1] and is usually related to increased urethral mobility and/or intrinsic sphincter deficiency (ISD). However, hypermobility and ISD frequently coexist [2]. The degree of urethral mobility and leak-point pressure are generally directly related.

Lack of inpatient beds, and patient and economic demands are driving the concept of minimally invasive, day-case surgery. The apparent cost-effectiveness of day surgery makes this an attractive form of treatment to purchasers of healthcare. Modifications in sling techniques have resulted in broader indications [3], reduced morbidity and a shorter hospital stay [4]. Autologous rectus fascia remains the ‘gold standard’ sling material for the surgical treatment of SUI [5]. However, the Pfannenstiel incision used for harvesting autologous fascia causes considerable postoperative pain and morbidity, thereby prolonging the hospital stay. One solution is to substitute the rectus fascia with a ready-made sling material. However, it is important that treatment safety and efficacy are not compromised. The main disadvantage of using a synthetic substitute is the risk of urogenital tract erosion [6]. Porcine dermal collagen (Pelvicol™, Bard Urology, UK), a biological sling material with virtually no risk of erosion, might be used and implanted as a day-case procedure. Thus the aims of the present study were to assess the suitability for discharge of patients 10 h after the a Pelvicol pubovaginal sling (PVS) procedure, the factors (early complications) affecting time of discharge, and the short-term cure rate.

PATIENTS AND METHODS
Between June 2003 and December 2003, 40 consecutive patients with SUI were enrolled in this prospective study. Ethical approval for the study was obtained from the local Ethics Committee. Patients were recruited after a decision was made for anti-incontinence surgery. Definitions conform to the standards recommended by ICS [7], except where specifically noted. Our inclusion criteria were that patients had an American Society of Anesthesiologists physical status classification of I or II, urodynamically confirmed SUI, and informed consent. Patients with a history of UTI in the previous 6 weeks, neuropathic bladder, uterovaginal prolapse, detrusor instability and voiding dysfunction (maximum urinary flow rate <15 mL/s, pressure at maximum flow rate of >40 cmH₂O, postvoid residual urine volume,
PVR, of >50 mL) were excluded from the study.

All patients were evaluated before surgery by history, physical examination, urine analysis and urodynamic study. All patients had a pelvic examination to assess pelvic floor defects and bladder neck motion. After free uroflowmetry and measuring the PVR, all patients had medium-fill subtracted cystometry using a 6 F double-lumen bladder catheter and a cuffed, air-filled 4 F rectal catheter. Cystometric variables measured included sensation, presence of detrusor instability, compliance and capacity. Urethral sphincter competence was assessed while semi-recumbent or standing, using the Valsalva manoeuvre or cough, at 50 mL intervals from 150 mL of filling, to obtain the abdominal leak-point pressure. Patients also completed the King's Health Questionnaire (KHQ) [8] and the 36-item Short-Form Health Survey (SF-36) quality-of-life (QoL) questionnaire [9]. Explanatory pamphlets were given to each patient, and they were counselled about the possible need for clean intermittent self-catheterization (CISC) after surgery, and briefly taught the technique. Patients were admitted with a planned overnight stay.

All sling operations were scheduled on a morning operating list. Before surgery all patients received thromboprophylaxis with subcutaneous enoxaparin 20 mg and antibiotic prophylaxis with intravenous ceftriaxone 1 g and gentamicin 240 mg. In all procedures patients were under general anaesthesia, with surgery by one urologist (H.D.F.).

The patient was placed in the modified lithotomy position in Allen's stirrups. After antisepsic dressing and draping, a 14 F Foley catheter was inserted. The sling was prepared using a 7 × 2 cm Pelvicol strip secured at each end with a 0 nonabsorbable polypropylene suture. Two small suprapubic stab incisions were made 5 cm apart just above the symphysis pubis. Then, a vertical 2.5 cm anterior vaginal wall incision was made. After paraurethral dissection, a Yachia needle was passed through the suprapubic stab incision and guided digitally behind the pubic ramus into the vaginal incision bilaterally. One end of the polypropylene suture was then passed through the eyelet in the needle, that was then withdrawn upwards. The procedure was repeated on the opposite side and the catheter removed. Cystoscopy was used to exclude any bladder injury. The sling was then placed under the proximal urethra at the urethrovesical junction. The sling sutures were then tied loosely over the rectus sheath on one side after subcutaneous transfer of one polypropylene suture across to the other incision. In patients with ISD the sling was tied with appropriate tension. Skin incisions were closed with absorbable suture and the bladder emptied. Suprapubic and vaginal wounds were infiltrated with local anaesthetic (20 mL of 5 mg/mL levobupivacaine). The patients were returned to the ward with no urinary catheter and a vaginal balloon pack was used for only 3 h after the operation. The operative duration and intraoperative blood loss were recorded, with any complications.

After surgery, NSAIDs such as intravenous parecoxib 40 mg, paracetamol suppository 1 g, diclofenac suppository 100 mg and oral nimesulide 100 mg, were used for pain control; opioid analgesia was avoided. Intravenous fluid was continued with solution-18 at 125 mL/h until the patient was able to drink fluid freely. All patients were instructed to report to a nurse as soon as they had a sensation to void after the pack was removed. They were then encouraged to void, and to use CISC if they failed to void spontaneously. In the absence of a spontaneous void within 6 h after surgery, CISC was used to avoid overdistension of the bladder. The catheterized volume was never >500 mL.

Patients were assessed at 4, 10 and 24 h after surgery for pain intensity using a visual analogue scale (VAS, 0 = no pain, 10 = worst pain). The interval to spontaneous voids, bladder emptying efficiency (EE) and early complications were also recorded. The suitability for discharge was assessed at 10 h after the procedure.

Our day-surgery unit opens at 09.00 hours (surgery at 09.00 h) and closes at 20.00 hours, which gives patients 10 h (allowing 1 h for surgery and recovery) in which to void efficiently in preparation for discharge. After each void, the voided volume (VV) and PVR were measured, the latter using CISC. The EE was calculated as W/(VV + PVR) × 100. Efficient emptying was defined as an EE of ≥75% [3]. Patients were considered suitable for discharge from hospital when emptying efficiently or when they could use CISC confidently with adequate pain control and had no significant complications.

Patients were further evaluated at 6 weeks, 3 and 6 months after surgery in the outpatient clinic. At each visit, patients were assessed by history and physical examination, and a validated questionnaire [10] (Appendix); they also completed the KHQ and SF-36 QoL questionnaires at the 6-month follow-up. Surgery results were classified as 'cured' when the patient reported no leakage of urine under any circumstances and no incontinence on a cough-stress test. 'Improved' was defined as a reduction of half or more in incontinence and no leakage on cough-stress test. 'Failure' was defined as a reduction of less than half in incontinence and or leakage on a cough-stress test [11]. A full urodynamic study was only used if the PVS failed.

The primary outcome measure was the suitability for discharge 10 h after surgery, based on the EE, no significant complication and adequate pain control after surgery. Secondary outcome measures were the time intervals to the first three spontaneous voids, EE of the first three voids, time required to achieve an EE of ≥75%, the VAS pain score soon after surgery, perioperative complications and short-term (6-month) SUI cure rate.

Data obtained from case report forms were transferred to a computer spreadsheet and entries then checked for any errors. All data were tested where appropriate for normality. The statistical significance was assessed using Student’s t-test, Fisher’s exact test or Wilcoxon matched-pairs test where appropriate, with P < 0.05 considered to indicate significant differences.

RESULTS

Table 1 shows the baseline characteristics of the study population; 13 patients (33%) had ISD. The operation was a primary procedure in 33 (83%) women and secondary in seven (18%). Previous surgery included one periurethral collagen injection, two Kelly plications, two Stamey vesicopexies, one rectus fascia pubovaginal sling and one Burch colposuspension. The median (range) preoperative EE was 100 (94–100%).

The variables assessed during and after surgery are shown in Table 2. The median
DAY-CASE SLING SURGERY FOR STRESS URINARY INCONTINENCE

Table 1. The patients’ characteristics, as the median (range) or n (%).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>46 (28–66)</td>
</tr>
<tr>
<td>Parity</td>
<td>3 (1–7)</td>
</tr>
<tr>
<td>Vaginal delivery</td>
<td>38 (95)</td>
</tr>
<tr>
<td>Caesarian section</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Incontinence starting after delivery</td>
<td>25 (62.5)</td>
</tr>
<tr>
<td>Duration of symptoms, years</td>
<td>5 (1–25)</td>
</tr>
<tr>
<td>Preoperative pad use</td>
<td>3 (1–6)</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>17 (42.5)</td>
</tr>
<tr>
<td>Using HRT</td>
<td>8 (20)</td>
</tr>
<tr>
<td>Previous hysterectomy</td>
<td>8 (20)</td>
</tr>
<tr>
<td>Previous incontinence surgery</td>
<td>7 (17.5)</td>
</tr>
<tr>
<td>Abdominal leak-point pressure, cmH2O</td>
<td>85 (29–164)</td>
</tr>
<tr>
<td>Patients with ISD</td>
<td>13 (32.5)</td>
</tr>
</tbody>
</table>

*Excluding six patients discharged on CISC.

Table 2. Operative and postoperative variables, as the median (interquartile range) or n (%).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operative duration, min</td>
<td>30 (25–35)</td>
</tr>
<tr>
<td>VAS pain score in first 10 h after surgery</td>
<td>3.5 (0–5)</td>
</tr>
<tr>
<td>EE at 10 h, %</td>
<td>61 (40–80)</td>
</tr>
<tr>
<td>*Time to EE ≥ 75%, h</td>
<td>13 (10–21)</td>
</tr>
<tr>
<td>*Number of voids to EE ≥ 75%</td>
<td>3 (2–4)</td>
</tr>
<tr>
<td>Number of patients with EE ≥ 75% at 10 h</td>
<td>16 (40)</td>
</tr>
</tbody>
</table>

*Number of voids to EE ≥ 75% (light green) for the first (green), second (red) and third (open bars) voids.

The differences in EE for the first three voids are shown in Fig. 1. The proportion of patients with an EE of ≥75% increased significantly from the first void to the second (Fisher’s exact test; P = 0.002), but the proportion showed no further significant increase from the second to third void (P = 0.381).

The cumulative distribution of time to voiding and an EE of ≥75% is shown in Fig. 2. Although 20% of the patients had their first void within 5 h, only 2.5% achieved efficient emptying. None of the patients had their second void within 5 h after surgery. Nearly two-thirds of the patients had their second void at 6–10 h and 40% achieved efficient emptying; 70% had efficient emptying within 24 h. The median (range) duration of hospital stay was 1.5 (1–3) days.

The mean EE 10 h after surgery was significantly higher in those with no ISD than in those with ISD (70% vs 39%, P = 0.001, t-test). Although 15 of 27 (56%) of the patients with no ISD had an EE of ≥75% at 10 h after surgery, only one of 13 of those with ISD had (P = 0.014, Fisher’s exact test), thus patients with ISD are significantly less likely to have an EE of ≥75% at 10 h after surgery. The mean EE 10 h after surgery in patients aged <60 years was greater than in those >60 years old but the difference was not significant (62% vs 40%, P = 0.113, t-test). If efficient emptying was defined as a EE of 50% then 24 (60%) patients were emptying efficiently 10 h after surgery. Overall, 40% of patients had a pain score of 0 (i.e. no pain) 10 h after surgery; one patient had a VAS pain score of 10 at 10 h, but she was mobile, emptying efficiently and was dischargeable; age and pain score did not affect the EE.

There were no major intraoperative complications and no bladder perforations. Two patients had a small amount of vaginal bleeding immediately after removing the vaginal pack (no actions was necessary and both settled on conservative management). One patient had significant nausea and vomiting soon after surgery and another was drowsy even 10 h after surgery. Of the six patients who were discharged on CISC, four achieved an EE of ≥75% within 7 days of discharge, and one each within 10 days and 14 days; no patient required urethrolysis.

There was one superficial abdominal wound infection and one abdominal wound haematoma, both resolving with conservative management. Three patients developed symptoms suggestive of UTI within 6 weeks of discharge and all were successfully treated with antibiotics by their family doctor. Two patients complained of intermittent left-sided deep pelvic pain for 3 months, but there was no obvious cause for this and both settled spontaneously with time.

The outcome of the PVS procedure is shown in Table 3. All patients were followed for up to 2 years.
6 months, and none were lost to follow-up. At the 6-week follow-up, there were no failures; at 3 months, three women reported further improvement of their condition from ‘improved’ to ‘cured’ and four reported deterioration of their SUl from ‘complete cure’ to ‘improved’. Two ‘improved’ women remained the same. One ‘cured’ woman was reclassified as ‘failure’ because of urgency and urge incontinence at the 3-month follow-up, although a urodynamic study showed no SUl or detrusor instability. She was treated with anticholinergic medication and physiotherapy, with some improvement of continence at the 6-month review, but was still considered a failure, as her improvement was less than half.

At the 6-month follow-up, one woman reported further improvement of her condition and she was reclassified as ‘cured’, and one had mild worsening of her continence from ‘cured’ to ‘improved’. Five women remained unchanged, as ‘improved’. Three more women were reclassified as failures after being reported as ‘cured’ at the 6-week and 3-month follow-up. Two had pure SUl and a third had pure detrusor instability on urodynamic study. At the 6-month follow-up, 10 (25%) women reported persistent urgency and two (5%) women developed de novo urgency. QoL measures showed significant improvements in four of the eight domains of the SF-36 and in seven of the eight domains of the KHQ at the 6-month follow-up (Fig. 3).

**DISCUSSION**

Advances in day-case anaesthesia and development of minimally invasive surgical techniques can be expected to continue. Day-case surgery has presented a new set of challenges and goals for surgeons. The success of day-case surgery depends largely on the nature of the surgery, effective control of postoperative pain and minimization of anaesthetic side-effects, e.g. sedation, nausea and vomiting.

In the present study, 40% of patients emptied efficiently and were suitable for discharge within 10 h of surgery. Only 10% of the patients had efficient emptying in their first void (Fig. 1). This shows that even with a loose sling, most patients have early emptying difficulty. This suggests that either even a loose sling is potentially obstructive or that other factors such as anaesthesia, pain or effects of local dissection influence voiding. With the present study protocol the median pain score was low, so pain was unlikely to be the cause of early emptying difficulty.

The present data also show that, although 68% of the patients had their second void within 6–10 h after surgery, only 20% had their first void within 5 h, and 10% took >10 h for their first void. If the threshold of EE for discharge were reduced to 50%, then 60% of patients could have been discharged. However, we do not know if an EE of ≥50% is an acceptable threshold. The implications of these findings for a typical day-surgery unit open from 08.00 to 17.00 hours is that a patient will have only 7 h after surgery in which to void efficiently (allowing 2 h for preparation, surgery and recovery). From the present data, only four patients (10%) would be suitable for discharge at 17.00 hours, and even if we had chosen a 50% EE as the threshold, only 14 (35%) would be suitable for discharge on the same day. In the USA, medical insurance considerations dictate <24 h as a threshold for inpatient ambulatory surgery; applying that threshold to the present patients, then 28 (70%) would have been eligible for discharge.

A standardized method to measure intraoperative sling tension has not yet been developed, although many techniques have been proposed. These techniques are limited because of technical difficulties [12,13] or because of the questionable relevance of procedures such as cough-stress test under regional anaesthesia. Moreover, in a study by Wang and Chen [14], nearly 45% of patients were unable to leak urine during a cough test in the dorsal lithotomy position. As there is no exact method of determining how much tension to put on the sling during surgery, the surgeon must rely chiefly on experience to make the judgement [3,4]. However, we found that patients with ISD were unlikely to achieve early efficient emptying and thus would not be suitable for discharge as day-cases. This is almost certainly because of higher applied sling tension resulting in outlet obstruction.

Difficulty in bladder emptying after anti-incontinence surgery is easily characterized by measuring the EE. The advantage of using EE as the prime measure of emptying difficulty is its simplicity and clinical relevance soon after surgery. In contrast to the PVR, which measures the amount of urine left after a void, the EE takes the pre-void bladder volume into account and is a more objective way to quantify bladder-emptying difficulty.

Although Ulmsten et al. [15,16] reported that most of their patients were discharged one day after an ambulatory procedure for SUl (tension-free vaginal tape), Nilson et al. [17] reported that 80% of the women in their study were discharged on the afternoon of the operation. In another study [18], 17 of 40 (43%) patients were discharged on the same day after a porcine dermal sling procedure. In all three studies there was no information on the time required to first spontaneous void and EE. The difference in the present study for day-case discharge rate reflects our stricter study protocol and discharge criteria.

There is wide variation in the use of catheters and vaginal packs after sling surgery. Although we used a vaginal pack for only 3 h, only two patients reported a small
DAY-CASE SLING SURGERY FOR STRESS URINARY INCONTINENCE

amount of vaginal bleeding soon after surgery and neither required intervention.

Only 10% of the present patients were willing to use CISC within 10 h after surgery and required assistance from a nurse. More extensive preoperative training might improve early ability with CISC and this might in turn improve the suitability for discharge. Furthermore, sedative side-effects of anaesthetic drugs are also an important hindrance to early patient mobility and CISC. Another possible solution would be to discharge patients with a short-term indwelling catheter and bring them to the day-surgery unit after 2–3 days. This would obviously mean another hospital visit and extra cost. Moreover, many of the present women were unwilling to go home with an indwelling catheter on the day of surgery.

Opioid analgesia after surgery might be associated with nausea, vomiting, increased time to tolerate oral fluids, sedation and urinary retention [19,20]. To avoid such possible interference after surgery we used NSAIDS instead of opioids. With our protocol, postoperative pain was never a limiting factor for discharge. Only two patients (5%) were unsuitable for discharge because of anaesthetic problems, and neither of these emptied efficiently.

Using QoL questionnaires and physical examination, overall SUI was cured or improved in 90% of the present patients at the 6-month follow-up. These cure rates are similar to those of other published series. The short-term overall cure rate using the Pelvicol sling is comparable with that of the autologous rectus fascial sling [21].

The present surgery was carried out by one urologist with a special interest in this field, and this might reduce the external validity. This bias would rather reinforce our findings of limitations to the day-case sling surgery approach. This was a prospective observational study; the objective was to provide preliminary estimates of variables and to generate hypotheses for testing in larger multicentre randomized trials where practical. Calculations of sample sizes based on this study can be used for further trials.

The present findings have four implications for clinical practice. First, only 40% of patients are suitable for Pelvicol day-case sling surgery; even patients considered ideal for a minimally invasive day-case sling could expect a significant risk of an overnight stay, which might be an unacceptable proposition because of increased unplanned hospital readmission. Second, early postoperative bladder emptying inefficiency is the main limiting factor; excluding patients with ISD and possibly decreasing the EE threshold to 50% would improve eligibility for discharge. Third, postoperative pain is not a limiting factor for day-case patient discharge. Finally, short-term results with the porcine dermal sling are similar to those with the autologous fascial sling.

ACKNOWLEDGEMENTS

This work was supported by educational grant from the National Institute of Health Sciences (NIHS), Limerick, Ireland and Pfizer Sales Ireland.

CONFLICT OF INTEREST

None declared. Source of funding: National Institute of Health Sciences and Pfizer, Ireland.

REFERENCES

16. Nilsson CG, Kuva N. The tension-free
vaginal tape procedure is successful in the majority of women with indications for surgical treatment of urinary stress incontinence. BJOG 2001; 108: 414–9


Correspondence: Hugh D. Flood, Department of Urology, Mid-Western Regional Hospital and National Institute of Health Sciences, University of Limerick, Ireland. e-mail: hflood@mwb.ie

Abbreviations: SUI, stress urinary incontinence; ISD, intrinsic sphincter deficiency; PVR, postvoid residual urine volume; KHQ, King’s Health Questionnaire; SF-36, The 36-item Short-Form Health Survey; Gol, quality of life; CISC, clean intermittent self-catheterization; EE, bladder emptying efficiency; VAS, visual analogue scale; VV, voided volume.

EDITORIAL COMMENT

The authors concluded that only 40% of patients were suitable for Pelvicol day-case sling surgery. Unfortunately the underlying principle reported here is not new. Sling surgery (even conventional sling surgery) has been used on a day-case basis, and usually is in North America, and the introduction of mid-urethral tapes has meant that a very large proportion of sling surgery is on day-cases. To facilitate this, patients may need to learn CISC or be prepared to go home with an indwelling catheter; sometimes patients are not ready to go home. In this paper the authors identified only 40% of patients who were suitable for day-case sling surgery, but this would not have been the case had the women been taught CISC or sent home with an indwelling catheter. What the authors showed is that voiding function returns gradually during the first few hours after inserting a sling, and that bladder emptying improves quite rapidly.

LINDA CARDOZO

APPENDIX

Postoperative questionnaire [10]

1. How much leakage of urine do you have now?
   A. None
   B. Mild
   C. Moderate
   D. Severe

2. If you do now leak urine, how does it usually occur?
   A. Mostly with coughing, sneezing or physical activity
   B. Usually not with physical activity, but leakage occurs suddenly with an urge to urinate before it can be controlled
   C. Leakage of urine often occurs in both of the situations described above
   D. Not sure when leakage occurs

3. How much improved is your urinary leakage compared to before sling operation?
   a. 100% better
   b. 90% better
c. 80% better
d. 70% better
e. 60% better
f. 50% better
   g. 40% better
   h. 30% better
   i. 20% better
   j. 10% better
   k. the same
   l. worse than before the surgery

4. Do you wear any protective pads for urine leakage?
   A. Yes
   B. No

5. If you are wearing pads, how many do you use in 24 h?

6. How often do you urinate during the day?
   A. More often than once every hour
   B. Every 1–2 h
   C. Every 3–4 h
   D. Less often than once every 4 h

7. How many times per night do you wake up from sleep to urinate?

8. If your incontinence returned after sling operation, how long after surgery was it?

9. If your incontinence returned after sling operation, how did it happen?
   A. Gradually over months
   B. Suddenly over a few days or week

10. Do you currently use a catheter to empty your bladder?
    A. Yes
    B. No

11. Do you get usually the urge to urinate?
    A. Yes
    B. No

12. Since your surgery, do you have problems with pelvic pain?
    A. Yes
    B. No

13. If you are having intercourse, is it painful?
    A. Yes
    B. No
    C. Not sexually active

14. Overall, how satisfied are you with the results of your sling surgery?
    0_1_2_3_4_5_6_7_8_9_10
    Not satisfied
    Very satisfied

15. Knowing what you know now, would you have the sling surgery again?
    A. Yes
    B. No

16. Would you recommend the sling surgery to your friend?
    A. Yes
    B. No
    C. Not sure.
A stereological analysis of fibrosis and inflammatory reaction induced by four different synthetic slings

MARCELO THIEL, PAULO C. RODRIGUES PALMA, CÁSSIO L.Z. RICCETTO, MIRIAM DAMBROS and NELSON R. NETTO Jr
Division of Urology, Universidade Estadual de Campinas, and Hospital Estadual Sumaré, Campinas, SP, Brazil
Accepted for publication 22 November 2004

OBJECTIVES
To analyse quantitatively, using stereological methods, the density of the collagen fibres induced by four types of sling materials, and verify by a histopathological analysis the corresponding inflammatory reaction, as fibrosis secondary to sling implantation is considered responsible for restoring urethral support and re-establishing continence in women with stress urinary incontinence, and new synthetic materials that promote adequate fibrosis with the least intensity and duration have been proposed to substitute the aponeurotic sling.

MATERIALS AND METHODS
The study comprised 70 female virgin Wistar rats divided into three groups: group A (30 rats) had 8 4 mm strips of silicone and porcine small intestine submucosa (SIS) implanted in the abdominal subcutaneous layer; group B (30 rats) had 8 4 mm strips of GAL implanted the abdominal subcutaneous layer; while a control group of 10 rats had dissection of the abdominal submucosa, as follows: group A (30 rats) had 8 4 mm strips of polycaprolactone and polylactic acid copolymers and monofilament polypropylene (PLP) implanted the abdominal subcutaneous layer; while a control group of 10 rats had dissection and suturing with 5/0 Nylon in the abdominal subcutaneous layer, as used to fix the strips in the other rats. Picro-Sirius staining was used to assess collagen fibres, and haematoxylin-eosin for the histopathological study. At 7, 30 and 90 days after surgery, 10 rats from each group were killed and assessed.

RESULTS
After 7 days all the materials induced a moderate inflammatory reaction that did not differ from that in the control group. At 30 days there was no difference between the control and polycaprolactone and polylactic acid copolymers, having the least inflammatory reaction. PLP and silicone produced a moderate inflammatory reaction, while the porcine SIS induced a more intense reaction. At 90 days there was a more intense inflammatory reaction in polycaprolactone and polylactic acid copolymers and monofilament polypropylene (PLP) implanted the abdominal subcutaneous layer, which again were no different. During this period the inflammatory reaction induced by SIS was greater. The stereological analysis indicated that collagen fibres induced by polycaprolactone and polylactic acid copolymers and PLP were less dense (61% and 65%, respectively), and significantly less than with silicone (89%) and SIS (86%).

CONCLUSION
PLP was the best nonabsorbable material as it induced a less intense inflammatory reaction than the other tested materials. As porcine SIS was completely absorbed the intense fibrosis induced is useful, as it is exclusively responsible for the urethral support later after surgery.

KEYWORDS
fibrosis, sling, materials, stress urinary incontinence

INTRODUCTION
Suburethral slings initially used for treating stress urinary incontinence were created from grafts taken from patients, and promoted organized fibrosis that reinforced the sphincter mechanism through improved suburethral support [1]. Currently, several materials are available [1,2] for this purpose, e.g. mono- and multifilament polypropylene (PLP) mesh, porcine small intestinal submucosa (SIS), human dermal matrix, and other materials being continuously developed. Some of these materials have been tested and rejected, e.g. PTFE and bovine pericardium.

The material that provides the best adequate long-lasting suburethral support with a low risk of local complications, e.g. sclerosis, infection and extrusion, has still not been defined. To date no study has objectively compared the intensity of fibrosis produced by different materials. Fibrosis is considered a good indicator of suburethral support, that substitutes for weakened natural ligaments and promotes the coaptation of the urethra under stress.

The purpose of the present study was to experimentally assess the intensity of fibrosis based on the volumetric density of the collagen fibres induced by four different materials used in the manufacture of slings, and to qualitatively determine the characteristics of the inflammatory reaction that occurs during its integration with the host tissue.

MATERIALS AND METHODS
The study comprised 70 female virgin Wistar rats (8 weeks old, mean 250 g), maintained in a controlled environment (25 ± 2 °C; exposed to a daily light cycle for 12 h) and with free access to water and food. The study was conducted in accordance with the Guide for the Care and Use of Laboratory Animals published by the US National Health Institute (Publication 85–23, revised 1985) and the Animal Protection Committee of our University approved the protocol.

Four types of material were compared; PLP, porcine SIS, silicone, and copolymers of polylactic acid and polycaprolactone (GAL). The animals were randomly divided into three groups and had materials implanted into the abdominal submucosa, as follows: group A (30 rats) had 8 4 mm strips of silicone and polycaprolactone, group B (30 rats), strips of GAL and PLP of the same dimensions, and a control group (10 rats) had dissection of the subcutaneous tissue and suturing with...
The quantitative measure was obtained using a light microscope and the fibres counted at ×400 magnification in 10 random microscopic fields in each group [4].

TABLE 1 The degree of inflammatory infiltration (absent/mild/moderate/severe) for each material after 7, 30 and 90 days. At 7 days there was no significant difference among the groups, at 30 and 90 days the SIS produced the most intense inflammatory reaction

<table>
<thead>
<tr>
<th>Group</th>
<th>7 days</th>
<th>30 days</th>
<th>90 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0/2/7/1</td>
<td>1/8/1/0</td>
<td>7/2/0/0</td>
</tr>
<tr>
<td>A SIS</td>
<td>0/1/8/1</td>
<td>0/1/4/5</td>
<td>0/4/2/4</td>
</tr>
<tr>
<td>A silicone</td>
<td>0/3/6/1</td>
<td>0/4/5/1</td>
<td>0/6/4/0</td>
</tr>
<tr>
<td>B GAL</td>
<td>0/2/5/3</td>
<td>0/7/3/0</td>
<td>4/3/2/0</td>
</tr>
<tr>
<td>B PLP</td>
<td>0/2/5/3</td>
<td>0/3/7/0</td>
<td>2/3/5/0</td>
</tr>
</tbody>
</table>

DISCUSSION

Slings are used to provide urethral support in patients with stress urinary incontinence, because the suburethral ligation that usually provide this support are weak [5]. Therefore, long-lasting suburethral support depends on the biomechanical characteristics of the material used to make the sling, as well as its capacity for inducing a reaction in the host that produces fibrotic support, which represents the main element of long-term support, especially in biological or absorbable synthetic slings [6].

Slings not only fulfill physiopathological requirements but are also less invasive and
help the patient to rapidly return to normal activities, with a favourable outcome in the medium-term. A previous study [7] aimed to determine the biomechanical characteristics of slings, including those of synthetic (Gore-Tex™ and PLP), cadaveric (decellularized and frozen skin, γ-ray irradiated fascia) and autologous materials (skin, rectus fascia and vaginal mucosa). When the entire strip of material was tested, the cadaveric fascia had the best performance, followed by the synthetic materials and last the autologous tissues ($P < 0.05$). When used as a patch, the synthetic materials were significantly better than the autologous and cadaveric fascia ($P < 0.05$). Although this analysis is important, it cannot be considered conclusive, as the final biomechanical characteristics of the sling may significantly change after incorporation by the host. As there are many materials now available with several different characteristics, the present study aimed to verify the tissue reactions induced by each material after implantation. Nonabsorbable synthetic materials generally present a greater risk for urethral erosion, but there is no consensus about the safest material. Theoretically, it is recommended that any sling should induce a minimum inflammatory reaction related to the capacity of promoting urethral support, which may depend to greater or smaller degree on local fibroid reaction [8]. A previous study comparing the changes in patients who had autologous, aponeurotic and PLP slings implanted concluded that although the outcomes related to urinary incontinence were similar, the synthetic material triggered a greater reaction in the local tissue, which was probably the result of a delayed hypersensitive immune reaction that could be extensive or not, depending on the biocompatibility of the material being used [9].

To identify factors associated with synthetic sling rejection, 428 sling were implanted by gynaecologists who used PTFE or PLP slings. The minimum follow-up in these 386 women was 24 months. Rejection or associated symptoms occurred in 47 women (12.2%). After introducing preoperative prophylactic antibiotics against anaerobes, and antiseptics with chlorhexidine acetate, there were fewer complications. There was no relationship between rejection and sling material, age or concomitant prolapse [10]. Except for the usual antiseptic procedures, no prophylactic antibiotics were used in the present study, to avoid any interference in the diagnoses of subsequent infections.

The main characteristic of porcine SIS is its behaviour as a collagen matrix for the growth of host tissue. After a prolonged period it induces remodelling and complete substitution of the surrounding recipient tissue, differing from simple random post-traumatic fibrosis. Preclinical studies of this biomaterial indicated that it has a greater resistance to bacterial infection than synthetic grafts [11], because of rapid neovascularization soon after implanting [12]. A SIS pubovaginal sling was used in 152 patients [13]; after 4 years of follow-up, 93.4% were still continent. However, 50.7% had urge incontinence, and the frequency was variable and persistent in some until much later. There were no reports of infection, erosion or rejection.

A sling material developed using biodegradable polydioxanone and polyactic acid copolymers with a structure similar to absorbable surgical suture was also analysed. The substitution of the host fibrous tissue during scarring is a characteristic of this material. A previous unrandomized study assessed the use of this sling in 11 patients and an early follow-up assessment showed that eight of the patients were continent, in accordance with the subjective assessment criteria [14].

Although silicone has been widely used in prostheses for several years, very little is known about its behaviour when used in slings. Only one previous study has reported a case of a urethrovaginal fistula attributed to the use of silicone [15].

The present histopathological assessment of the samples showed clearly that the intensity of the inflammatory reaction induced by the various implant materials differed. The analysis at 7 days represented the early reaction to the implant, while those at 30 and 90 days mimic late and final integration stages, respectively. The results showed that during the first 7 days all materials induced a similar response and did not differ.

FIG. 1. Microscopic aspect of the implants after 90 days. SIS, silicone, PLP and GAL induced collagen fibres in 86%, 85%, 65% and 61% of the analysed area, respectively. (A) porcine SIS; (B) silicone; (C) monofilament PLP; (D) GAL (haematoxylin and eosin, x400).
significantly from the control group, but at 30 and 90 days this changed. After 30 days, the response to GAL was similar to that in the control for the inflammatory reaction, suggesting that there are unlikely to be inflammatory exudates and extrusion during this phase. PLP and silicone produced a more intense reaction than in the control and GAL, but less intense than that induced by SIS. After 90 days, there was a more intense reaction to all implanted materials; the stereological analysis showed that GAL had the least capacity for stimulating the production of collagen fibres. This is a long-term absorbable material, and thus this characteristic represents a potential disadvantage because the main element that provides long-lasting support is the fibrous tissue newly formed in response to the implant.

PLP stimulated an intermediate inflammatory reaction, greater than that of GAL and less than that of SIS and silicone. As it is currently the most used material, it is also the most studied for use in slings. Despite there being several clinical studies they rarely discuss aspects related to sling integration and reactions induced in the host tissue. A recent study [16] conducted on humans used tissue biopsy to compare polypropylene with another synthetic material, Mersilene, and verified minimal changes in the connective tissue at the site, which was in accordance with the findings of the present study. The advantage of using propylene instead of the other synthetic materials is its low rate of complications, which can be explained by the low intensity of tissue reaction to the implant, as confirmed here. Considering the good clinical results with PLP slings and the incorporation of this material, another conclusion suggested is its independence from newly formed local collagen in the long-term maintenance of continence. Hence, it can be inferred that the nonabsorbable PLP mesh is important in late postoperative urethral support. There has been speculation about the possible influence of PLP mesh pores (quantity and dimension) in relation to the predisposition to local infection and biocompatibility [17].

The degree of inflammatory reaction induced by silicone is similar to that of PLP. Nevertheless, the stereological analysis showed that the capacity to promote fibrosis around the graft (mean 85% volumetric density) was intense. Overall, reports on the use of silicone in slings characterize it as having the highest rate of graft complications and rejection [16], and a high rate of urethral or vaginal wall erosion, abscess or pseudocyst formation involving the graft [18]. These findings are attributed to the surface characteristics; silicone is smooth and not porous, contrary to polypropylene mesh. Nonetheless, the present analysis indicated that most of these features in clinical use are probably caused by the intense inflammatory response induced by the graft and the consequent local exudation and necrosis that make the site more susceptible to complications. Despite the high rejection rates for this type of implant, the same studies report high cure rates for urinary incontinence during a prolonged follow-up, even in women who have had the sling removed, and in those who had early removal of the implant at 4 weeks after initial surgery [18]. These apparently contradictory data are explained by the intense deposition and organization of collagen fibres around the graft, as noted here. These findings also reinforce the idea that acute stimulation of fibrosis around the implant is one of the factors responsible for the effectiveness of this technique, even with materials associated with a high rate of complications after surgery.

The most inflammation was provoked by SIS; the stereological analysis indicated that of all the tested materials, it was the greatest stimulus for the formation of collagen fibres (86% volumetric density), a little more than that of silicone and much more intense than the GAL or monofilament PLP. Although there are few clinical studies on this material, the results showed that treatment with this type of sling was highly effective and had the lowest complication rate [13]. This material can be considered an allograft, representing the only natural material analysed in the present study. The SIS surface is wrinkled and has pores, characteristics that differentiate it from silicone and more like PLP. However, it differs from the latter because after promoting the induction of new collagen tissue by the host tissue, it is completely absorbed later. The importance of these differences in clinical practice should be assessed by clinical assays before reaching a conclusion. Nevertheless, this material produced the highest stimulus for the formation of collagen fibres around the graft, that might guarantee long-term maintenance of continence after the procedure, an indispensable characteristic for a sling that is completely absorbed after some time.

Currently, more intensive research aimed at reducing complications is being conducted in the area of implantable urinary tract biomaterials, whether for use in endoluminal catheters, slings or even for partial or total organ substitution. With the development of in vitro cell culture techniques and tissue recovery through gene therapy, research on this aspect has changed recently. Therefore, similar experimental and prospective studies on biocompatibility have become increasingly necessary before these materials can be made available for general use. Hence, biomaterials may be associated in future with a low risk of infection, erosion, mineral deposition, migration of particles, secondary reactions, but with better durability.

In conclusion, urethral support, the main objective of any sling, depends on its specific resistance, determined by its physicochemical properties and the response induced in the host by the sling, represented by new local fibrous tissue. Therefore, the lower the persistence and specific resistance of the material, the greater its capacity for inducing a resistant support at the site. From the present study, PLP and SIS represent materials that combine these characteristics in a balanced and synergistic manner. The former is the most adequate nonabsorbable material because it induces an inflammatory reaction that is less intense than with other materials. As the SIS was completely absorbed after some time, the intense fibrosis is advantageous, as it is responsible for urethral support after surgery. Thus, in relation to the histopathological and stereological characteristics of the host integration process, PLP and SIS are the best alternatives for manufacturing slings, and better than silicone and GAL.

ACKNOWLEDGMENTS

This study was supported by grants from Coordenação e Aperfeiçoamento de Pessoal de nível superior (CAPES) and the Foundation for Research Support, State of São Paulo – FAPESP (Proc 01/11205–5). This paper forms part of a thesis submitted to the Department of Surgery of the Faculty of Medical Sciences, State University of Campinas, UNICAMP, in
partial fulfilment of the requirements for the PhD degree in surgery.

CONFLICT OF INTEREST
None declared.

REFERENCES
8 Bemelmans BL, Chapelle CR. Are slings now the gold standard treatment for the management of female urinary stress incontinence and if so which technique? Curr Opin Urol 2003; 13: 301–7
15 Shobeiri SA, Echols KT, Franco N. Sinus formation after insertion of a silicone-coated suburethral sling. Int Urogynecol J Pelvic Floor Dysfunct 2003; 14: 356–7

Correspondence: Marcelo Thiel, Rua Barão de Jaguara, 601, apto 122, Campinas SP Brazil CEP 13015–001. e-mail: thiel7@uol.com.br

Abbreviations: SIS, porcine small intestinal submucosa; PLP, multifilament polypropylene; GAL, copolymers of polylactic acid and polycaprolactone.
Sacral magnetic stimulation in non-inflammatory chronic pelvic pain syndrome

THOMAS LEIPPOLD, RAETO T. STREBEL, MIRJAM HUWYLER, HUBERT A. JOHN, D. HAURI and DANIEL M. SCHMID
Department of Urology, University Hospital Zurich, Switzerland
Accepted for publication 29 November 2004

OBJECTIVES
To prospectively evaluate sacral magnetic high-frequency stimulation as a treatment option for patients with non-inflammatory chronic pelvic pain syndrome (CPPS, category IIIB).

PATIENTS AND METHODS
Fourteen men with CPPS IIIB were treated with high-frequency sacral magnetic stimulation, with 10 treatment sessions once a week for 30 min at a frequency of 50 Hz. The National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) and quality-of-life index were determined before and after treatment.

RESULTS
All patients tolerated the stimulation well and 12 of 14 reported agreeable sensations during stimulation. There were no complications; only one patient did not complete the treatment course. The mean (range) total NIH-CPSI score did not change with treatment, at 27 (18–38) before and 27 (4–40) after treatment. Moreover, there was no sustained effect on the mean scores for pain, micturition complaints or quality of life.

CONCLUSIONS
High-frequency sacral magnetic stimulation in patients with CPPS IIIB only reduces pain during stimulation, with no sustained relief of symptoms. Therefore, intermittent sacral magnetic stimulation cannot be recommended as a treatment option for CPPS IIIB.

KEYWORDS
chronic pelvic pain syndrome, chronic prostatitis, sacral magnetic stimulation

INTRODUCTION
Pelvic pain is the predominant symptom in patients with chronic prostatitis. In 1995, the American National Institute of Diabetes and Digestive and Kidney Diseases Working Group on prostatitis proposed the term chronic pelvic pain syndrome (CPPS) [1]. The new classification according to the National Institutes of Health (NIH) supports the diagnosis and management of these patients, being: I, acute bacterial prostatitis; II, chronic bacterial prostatitis; IIIA, inflammatory CPPS; IIIB, non-inflammatory CPPS; IV, chronic asymptomatic prostatitis. It has been estimated that about half of men have prostatitis at some time in their life [2], and recently published epidemiological studies show that the prevalence is 5–12% [3,4].

Prostatitis is the most common reason for a man aged <50 years to consult a urologist, accounting for 8% of all urology visits in the USA [5]. The effect on a patient’s quality of life is substantial, with similarities to patients who have had a recent myocardial infarction [6]. Bacterial infection of the prostate is the cause in only 5–10% of patients with chronic prostatitis [7,8]. Non-inflammatory CPPS (according to NIH definition, CPPS IIIB) is characterized by a painful syndrome of the pelvis with no evidence of inflammation in prostatic secretions or seminal fluid [9]. Usually patients present with protracted pelvic pain, perineal discomfort and substantial LUTS. Most patients report a history of multiple antibiotic treatments with no improvement and, consequently, have serious psychological disturbances [10]. The NIH Chronic Prostatitis Symptom Index (CPSI) is a validated tool to evaluate symptoms of pain, voiding and impact on quality of life [9].

To date, no evidence-based pathophysiological cause of CPPS IIIB has been suggested, and thus many therapies have been proposed, some of them with a doubtful rational basis. However, none of them has shown any permanent major relief of symptoms. It is generally thought that CPPS IIIB is a neuromuscular disorder of the pelvic floor/perineal complex [11]. Therefore, we determined the possible therapeutic effect of sacral high-frequency neuromodulatory magnetic stimulation on patients with CPPS IIIB.

PATIENTS AND METHODS
From September 2003 to May 2004, 14 men (mean age 49 years, range 26–65) and with a clinical diagnosis of CPPS IIIB were prospectively studied, after being evaluated using the NIH-CPSI. The mean (range) duration of prostatitis was 3 (1–8) years, and patients had consulted an average of two other urologists or general physicians. They had been treated with antibiotics for 10 (4–18) weeks during their history of CPPS.

Samples of the first-voided urine, midstream urine, expressed prostatic secretion and voided urine after massage were cultured. A prostatic swab or first-void and midstream urine were tested for Chlamydia trachomatis, Neisseria gonorrhoeae, Ureaplasma urealyticum, Mycoplasma hominis and Mycoplasma penetrans. The men were diagnosed with CPPS IIIB according to NIH criteria [2], i.e. high-power microscopy (>1000) of expressed prostatic secretion showed <10 leukocytes, bacterial growth was <10^3/mL of expressed prostatic secretion, and seminal fluid showed no significant bacterial growth and leukocyte counts. Urodynamic evaluation or anal rectoscopy were used when indicated.
Magnetic stimulation was applied with a MAG PRO X100 (Medtronic A/S, Skovlunde, Denmark) device. The magnetic stimulating coil was placed lumbosacrally on the patient while prone (Fig. 1), the final exact position of the coil being defined by the patient reporting a crawling feeling and muscle contraction during magnetic stimulation in the area of pain. Repetitive magnetic biphasic high-frequency stimulation was delivered for 30 min (50 Hz, 100 pulses in a train and an intertrain interval of 2 s). Patients had 10 treatment sessions once or twice a week. The NIH-CPSI was determined before and after the 10 treatment sessions.

RESULTS

CPPS IIIB was diagnosed in all 14 men; the magnetic stimulation was well tolerated and there were no side-effects. Twelve of 14 patients reported a distinct, agreeable and crawling feeling in the area of pain during stimulation. Thirteen men finished the 10 treatment sessions and one man stopped after the fourth, as he was unwilling to continue because the treatment was ineffective. Only one patient (who completed the 10 treatment sessions) reported an improved NIH-CPSI score, from 19 before treatment to 4 afterward; in 12 patients there was no overall benefit.

The mean total NIH-CPSI scores did not change with treatment, but remained at a similar level, with a mean (range) score of 27 (18–38) before treatment and 27 (4–40) afterward. The mean (range) pain score did not change significantly, at 12.4 (6–20) before and 12.7 (1–19) after treatment. The mean (range) voiding-complaint scores did not significantly decrease, from 6 (3–10) before to 5 (3–9) after treatment ($P = 0.226$). The mean (range) quality-of-life scores showed no beneficial effect, at 9 (6–12) before and 9.5 (3–12) after treatment.

DISCUSSION

CPPS is a common and debilitating problem that significantly impairs quality of life [12–16], but no evidence-based therapies are available. These patients usually consult several physicians and are often treated with different unsuccessful antibiotic trials. Furthermore, they can experience psychological problems and sexual dysfunction. Absence from work is extensive, and some patients never return to work [10]. However, the cause of CPPS remains unclear. Many procedures to treat CPPS or chronic prostatitis have been reported, the International Prostatitis Collaborative Network published a listing in order of priority of therapies that have at least some evidence or theoretical basis for treatment [17]. The pain-suppressive effect of low- (2 Hz) and high- (50–100 Hz) frequency peripheral electrical stimulation was evaluated in 1976 by Andersson et al. [18] in patients with chronic pain in the legs or back. High-frequency electrical stimulation of afferent nerve fibres is hypothesized to control pain by modulating the transmission of pain impulses [19]. High-frequency stimulation was reported to be more successful, although the effect was short lasting. Campbell and Long [20] implanted nerve-stimulating devices for pain control in 33 patients with various disabling chronic pain conditions; eight had excellent pain suppression and seven had intermediate success. The electrodes were placed on major nerves innervating the area of pain. Novak and Mackinson [21] implanted peripheral nerve stimulators in 17 patients following injury to a peripheral nerve, with excellent results in five and a good response in six. Siegel et al. [22] showed that transforaminal S3 and S4 sacral nerve stimulation could have beneficial effects on the severity and frequency of chronic intractable pelvic pain; nine of 10 patients had a decrease in severity of pain at a median follow-up of 19 months. John et al. [23] introduced a high-frequency electrostimulation device to treat CPPS IIIB, with temporary success in 10 of 12 patients. Urethro-anal stimulation was applied once a week for 10 sessions. Peters and Konstandt [24] showed a decrease in narcotic requirements by long-term sacral neuromodulation in 18 of 21 patients with refractory interstitial cystitis using an implanted device.

An electrical current through a coil induces a magnetic field and a changing magnetic field in turn induces an electric field. This physical law can be applied to allow noninvasive stimulation of the sacral roots using a magnetic field. Based on the cited reports, we postulated that repeated sacral high-frequency magnetic stimulation of afferent nerves supplying the pelvic floor and pelvic organs might temporarily or permanently relieve chronic pelvic pain. This hypothesis is supported by the observation that electrical sacral neuromodulation is successful for treating urgency and frequency syndromes [25]. Similarly, Yamanishi et al. [26] successfully treated six of eight patients with mainly neurogenic urge incontinence, using sacral magnetic neuromodulation.

Patients with CPPS have an altered sensation of perineal pain elicited by heat, which might represent a C-fibre mediated effect [27]. Equally, neurogenic and idiopathic forms of bladder overactivity are thought to be mediated by C-fibres [28,29]. In the present study, sacral magnetic neuromodulation in patients with CPPS IIIB did not improve pain, symptoms of micturition or quality of life. Although most patients reported agreeable sensations during stimulation, this effect did not translate into a sustained relief of symptoms. Only one patient did not complete the whole treatment course, although 12 of 14 had no benefit from the sacral magnetic stimulation. Presumably this low withdrawal rate can be explained by the ease of...
application, the lack of side-effects and most importantly, the desire for cure of this debilitating condition.

Interestingly, in a pilot study, sacral magnetic stimulation temporarily eliminated the pain in five patients with pudendal neuralgia, the effect lasting from 30 min to 56 days [30]. This pain-reducing effect might be explained by the different causes of the overlapping symptoms of CPPS and pudendal neuralgia. By contrast, peripheral afferent electrical nerve stimulation produced no symptom relief in patients with chronic prostatitis or intractable interstitial cystitis [31,32]. The failure to obtain sustained symptom relief by magnetic sacral stimulation in CPPS does not exclude a role for high-frequency magnetic sacral stimulation in CPPS IIIB only reduces pain relief in patients with chronic prostatitis or intractable interstitial cystitis. The pain-reducing effect might be explained by the different causes of the overlapping symptoms of CPPS and pudendal neuralgia. Indeed, during stimulation patients reported symptoms of CPPS and pudendal neuralgia.

High-frequency sacral magnetic stimulation in patients with CPPS IIIB only reduces pain during stimulation without producing a sustained relief of symptoms. Therefore, intermittent sacral magnetic stimulation cannot be recommended as a treatment option in CPPS IIIB.

CONFLICT OF INTEREST

None declared.

REFERENCES


Correspondence: Thomas Leippold, Department of Urology, University Hospital Zurich, Frauenklinikstr. 10, 8091 Zurich, Switzerland. e-mail: thomas.leippold@usz.ch

Abbreviations: CPPS IIIB, non-inflammatory chronic pelvic pain syndrome; NIH-CPSI, The National Institutes of Health Chronic Prostatitis Symptom Index.
Use of combined intracorporal injection and a phosphodiesterase-5 inhibitor therapy for men with a suboptimal response to sildenafil and/or vardenafil monotherapy after radical retropubic prostatectomy

JACK H. MYDLO, ROSALIA VITERBO and PAUL CRISPEN
Department of Urology, Temple University School of Medicine, Philadelphia, PA, USA
Accepted for publication 8 November 2004

OBJECTIVE
To report experience with combined therapy using intracorporal injection (ICI) of alprostadil and oral phosphodiesterase 5 (PDE-5) inhibitors for the minimally invasive treatment of erectile dysfunction (ED) after radical prostatectomy (RP), as PDE-5 inhibitors are effective but a few patients may have a suboptimal response.

PATIENTS AND METHODS
In a retrospective study, 34 men (aged 46–66 years) had a nerve-sparing retropubic RP and subsequent ED. Patients were titrated on sildenafil citrate or vardenafil to maximum doses. All had a suboptimal response after a maximum of eight doses of oral therapy and were then treated with ICI therapy using 15 or 20 μg alprostadil. Erectile function was assessed with the Sexual Health Inventory for Men (SHIM).

RESULTS
Of the 32 patients who continued combined therapy, 22 (68%) had an improvement in erectile function after ICI therapy, as assessed by the SHIM score. On follow-up, 36% of these patients used ICI therapy only intermittently, instead of regularly, as they felt that this was adequate enough for good results.

CONCLUSIONS
PDE-5 oral pharmacotherapy is the most commonly used effective therapy for ED but may not be as effective in patients who have radical surgery; the addition of testosterone patches may have side-effects or be considered a risk in patients with a history of prostate cancer. The use of ICI therapy as an adjunct or maintenance therapy to their oral medication may be another alternative in these patients.

KEYWORDS
erectile dysfunction, combined therapy, injection, prostate cancer

INTRODUCTION
Current therapy for erectile dysfunction (ED) includes penile re-vascularization, semi-rigid and inflatable penile prostheses, transurethral alprostadil urethral suppositories,
intracavernosal injection (ICI) therapy and oral pharmacotherapy. The use of the phosphodiesterase (PDE) type 5 inhibitors is currently the main effective and simple treatment, and they are the most commonly used agents. They result in increased levels of cyclic GMP and, combined with nitric oxide, lead to the relaxation of the corporal smooth muscle and consequent erection [1,2].

Recent data show that 18% of the prescriptions for PDE-5 inhibitors are written by urologists, while 82% are written by other physicians. Therefore, effective treatment for ED is now available to many physicians and patients, who previously perhaps may not have entertained invasive therapies [1–7]. PDE-5 inhibitor therapy has had a major impact on the effective and noninvasive treatment of ED, and these drugs have now been in use long enough to evaluate their effectiveness in real situations. Several reports now show that there is a small but significant proportion of men with a suboptimal response [7–10].

Combined therapy for men with a suboptimal response to PDE-5 inhibitor therapy was reported previously, and consists of sildenafil and intrarectal alprostadil (MUSE), or sildenafil and androgen supplementation if the patient has subtherapeutic levels of testosterone [11–15]. However, androgen supplementation after prostate cancer surgery may be considered controversial. Thus we assessed the efficacy of sildenafil and/or vardenafil with the booster effect of ICI therapy using alprostadil in men with ED after radical prostatectomy (RP).

PATIENTS AND METHODS

The study started with 49 men who had good erections before surgery, who had a nerve-sparing retropubic RP and who sought treatment for ED afterwards. These men were treated with either sildenafil or vardenafil. After having a suboptimal response from the maximum dosage of eight doses (100 mg for sildenafil, 18 men, and 20 mg for vardenafil, 16 men), these 34 patients were titrated to their maximum benefit from ICI therapy with alprostadil (either 15 or 20 μg). Once taught in the office, they used ICI at home.

The Sexual Health Inventory for Men (SHIM) was used before starting treatment with oral therapy; a score of 25 was considered normal and of ≤21 as associated with some degree of ED. The assessment of improved erectile function was based on an improved SHIM score. We also determined how long the patients continued on ICI therapy, and any side-effects and other issues related to its use. No other pharmacotherapeutic agents were used in these patients, e.g. MUSE suppositories or devices such as the penile occlusive ring.

RESULTS

Of the original 49 men who had nerve-sparing RP and oral therapy for ED, 15 were satisfied with their response to oral therapy; the remaining 34 patients (aged 46–66 years) were included in the study. Oral PDE-5 therapy led to some improvement in erectile function in most patients but we also ensured that the patients were re-educated in the proper use of their medication, i.e. that their pills were being taken on an empty stomach, at up to eight doses for the desired effect, and that the men were sufficiently aroused.

The patients tried PDE-5 therapy at home, first in private with erotic material instead of using it immediately with their partner. We find that this approach eliminates the psychological aspects of the pressure and expectations of the partner. Once this confounding variable is eliminated, it is easier to assess the efficacy of the drug for the couple. Those patients who were still dissatisfied with a less than optimal response were then re-evaluated with the SHIM questionnaire; there were no differences between sildenafil and vardenafil failures.

Initially the ICI therapy was administered by the physician and then patients were taught to inject themselves. Two patients withdrew from ICI treatment because of painful injections. Surprisingly, cost was not a factor to discontinue its use, especially if the results were beneficial. For several patients where health insurance did not cover both therapies, free samples were given.

In all, 22 of the 32 men (68%) reported having a much better erection with PDE-5 inhibitors after starting ICI therapy, based on responses from the SHIM questionnaire (Table 1). They also stated that ICI was helpful in maintaining the effectiveness of the PDE-5 inhibitor.

After 7 months, eight patients (26%) stopped using ICI therapy regularly because they claimed they had good erections with intermittent use. The regular users continued ICI monthly, after their third or fourth PDE-5 dose. Although several patients stated they had some soreness at the site of injection, they alternated the sides and continued ICI therapy.

DISCUSSION

Normal erectile physiology involves contributions from several organ systems; the vascular, endocrine and neuronal systems are crucial for normal erectile function [1]. Often more than one of these systems is deficient or damaged in men with ED. There are several potential ways to approach a patient with a suboptimal response to PDE-5 inhibitors. Combined therapy involving a PDE-5 inhibitor and a second agent, which targets another vascular, endocrine or neuronal pathway, may provide a better outcome in this selected group of patients. Several supplemental/combined therapies for men with a suboptimal sildenafil response have been described. These combined therapies include testosterone supplementation, a centrally acting dopamine agonist, intrarectal and ICI therapies [11–18].

The role of testosterone in men with ED is not clear; replacing testosterone alone in men with normal or low-to-normal levels of testosterone does not significantly improve erectile function. However, in patients with low levels of serum testosterone, supplementing testosterone in combination with oral sildenafil is beneficial in those with a suboptimal response to sildenafil alone [15].

Although serum testosterone levels and the incidence of prostate cancer have not been shown to be associated risks, in the present medicolegal climate supplementing with
testosterone should be used cautiously in patients who have a history of, or are at an increased risk for, prostate cancer [19–21]. Moreover, the testosterone dermal patches have been associated with a severe dermatitis in up to 35% of patients [22]. Patients with Parkinson's disease, cerebral vascular accidents, Alzheimer's disease and depression may also have ED [1,2,17].

The relationship between CNS pathology and ED may involve central neurotransmitters and neural hormones. Dopamine agonists are currently being investigated in the treatment of ED [16]. Apomorphine, a D1 and D2 receptor agonist, combined with sildenafil has been shown to increase intracavernosal pressure in the rat model [1,2].

Peripheral nervous system pathology is well known to adversely affect erectile function. The importance of an intact cavernosal innervation is shown by the high rate of ED after non-nerve sparing RP [21]. Medical treatment that directly addresses peripheral nervous system lesions is lacking.

Cavernosal smooth muscle relaxation is instrumental in erectile physiology; this is regulated by cytosolic Ca++ levels, and these are regulated by two second-messenger systems involving cGMP and cAMP. Pharmacological manipulation of these second-messenger pathways is currently used in the treatment of ED, in that PDE-5 inhibitors target the cGMP pathway, while the cAMP pathway is targeted by agents such as alprostadil. Targeting both second-messenger pathways with combined therapy may be beneficial in patients who have a suboptimal response to PDE-5 inhibitors alone [1,2,7].

Mydlo et al. [11] reported on the use of MUSE and sildenafil combined for those patients who had a suboptimal response with monotherapy. They reported an overall improvement of 114% using MUSE and sildenafil over either alone, using the International Index of Erectile Function questionnaire to assess the improvement in erectile function. Subsequently, they reported a high attrition rate because of the cumberoseness of using different medications 30 min apart, the urethral discomfort and the cost [12].

ICI is an effective alternative because it acts locally with no major systemic side-effects. The efficacy is reportedly 72–87% [13,14] but there is a high discontinuation rate of 37–76% caused by local side-effects or aversion to self-injection. McMahon et al. [14] studied the ability of sildenafil to salvage patients failing ICI therapy. They reported a 66% salvage rate in patients receiving sildenafil combined with ICI, but the effect of combined therapy was no better in them than for sildenafil alone. However, Shabsigh and Anastasiasidis [15,16] reported an 88% response rate in patients using ICI in whom sildenafil alone had failed. Other investigators reported the ‘booster’ effect of intermittent ICI in the office for patients with a suboptimal response to sildenafil [16–18]. Kaplan et al. [19] reported on the beneficial use of an α-blocking agent combined with ICI, suggesting that the synergistic effects of vascular dilatation and blockade of sympathetic inhibition may explain this response. This additional pharmacotherapy may be considered in future studies in those patients we are treating with combined PDE-5 inhibitors and ICI. However, this would further add to the cost of combined therapy, which may be prohibitive for the patient. Even more important is to consider the side-effects that can occur with the synergy of combined therapy, e.g. hypotension, priapism, headache, curvature of the shaft from repeated injections, etc. Each patient must be made aware that combined therapy has greater risks and side-effects because of the synergy.

Last, we noted that in patients with no prostate cancer who complain of ED resulting from their antidepressant medication, successful treatment with combined therapy led to less depressed patients, and consequently less antidepressant medication, which reversed their ED-antidepressant medication ‘cycle’ [17].

There were several limitations to the present study. First, there were relatively few patients and the study was not randomized or controlled. Therefore, no statistically significant conclusions can be drawn from the data. Second, although all these nerve-sparing RPs were performed by one surgeon (J.H.M.) there may still have been variation in the trauma to the nerves, either unilaterally or bilaterally. This could account for some variability in the results after surgery. Last, the follow-up was insufficient to determine how many more patients would stop taking ICI because of the side-effects, cost, loss of efficacy, loss of motivation or partner support. However, this small analysis should serve as a pilot for a larger, randomized sample study of patients.

The management of ED after RP is especially challenging; nerve-sparing techniques have improved potency rates after RP, but ED still occurs at a high rate. The response to sildenafil after RP is strongly influenced by nerve status at the time of surgery. Several reports show a significantly lower response to sildenafil monotherapy in patients undergoing RP than in controls [20–25]. Combined therapy may have a role in these patients.

In conclusion, in patients with ED after RP and with a suboptimal response to PDE-5 monotherapy, ICI and PDE-5 combined therapy may be a safe and effective alternative, using minimally invasive treatment.

CONFLICT OF INTEREST
None declared.

REFERENCES

9. Gralnek D, Wessells H, Cui H, Dalkin BL.
Differences in sexual function and quality of life after nerve sparing and nonnerve sparing radical retropubic prostatectomy. J Urol 2000; 163: 1166–70


11 Mydlo JH, Volpe MA, Macchia RI. Initial results utilizing combination therapy in patients with a suboptimal response to either alprostadil or sildenafil monotherapy. Eur Urol 2000; 38: 30–4

12 Mydlo JH, Volpe MA, Macchia RJ. Results from different patient populations using combined therapy with alprostadil and sildenafil: predictors of satisfaction. BJU Int 2000; 86: 1–6


Correspondence: Jack H. Mydlo, Department of Urology, Temple University Hospital, 3401 North Broad Street, Philadelphia, PA 19140, USA, e-mail: jmydlo@astro.temple.edu

Abbreviations: ED, erectile dysfunction; ICI, intracavernosal injection; PDE-5, phosphodiesterase type 5; MUSE, intraurethral alprostadil; SHIM, Sexual Health Inventory for Men; RP, radical prostatectomy.
The effect on erectile function of $^{103}$ palladium implantation for localized prostate cancer

ANTON PONHOLZER*, RENÉE OISMÜLLER†, CANATAY SOMAY‡¶, FELIX BÜCHLER†, ULRICH MAIER*†, ROBERT HAWLICZEK‡¶, MICHAEL RAUCHENWALD*† and STEPHAN MADERSBACHER*†

*Department of Urology and Andrology, Ludwig Boltzmann Institute for Urological Oncology, †Institute of Radio-oncology and Ludwig Boltzmann Institute for Applied Research in Radiation Oncology, Donauspital, Vienna, Austria

Accepted for publication 1 December 2004


OBJECTIVE

To determine in a prospective study the effect on erectile function of $^{103}$Pd brachytherapy for localized prostate cancer, using a validated questionnaire.

PATIENTS AND METHODS

Between July 1999 and April 2003, 113 men with localized prostate cancer were treated by permanent implantation of $^{103}$Pd seeds, of whom 78 with a follow-up of 30 months were included in this study. No patient received supplemental external beam radiation therapy. At baseline and 3-month intervals, erectile function (EF) was assessed by the EF domain score of the International Index of Erectile Function-15 (IIEF-15); 77% received (neo)adjuvant antiandrogen therapy for up to 3 months.

RESULTS

At baseline, 27 (35%) patients had no erectile dysfunction (ED; EF domain score 26–30), 24 (31%) had mild/moderate ED (score 11–25) and 27 (35%) severe ED (score 6–10). The mean EF domain score decreased from 17 to 12 ($P<0.001$) after 30 months. Overall, 52 men (67%, including those with severe ED at baseline) remained in the same ED category at 30 months after therapy as before, 12 (15%) deteriorated by one category, 14 (18%) by two or more, and no patient improved. Of the 27 patients fully potent (score 26–30) at baseline, 37% remained so after 30 months, 19% developed mild and the remaining 44% moderate/severe ED. In a multivariate analysis, neither age nor preoperative prostate-specific antigen level, prostate volume, DB9, hormonal treatment, diabetes, smoking or hypertension were predictive of preserving potency ($P>0.05$).

CONCLUSIONS

There was a high prevalence of pre-existing ED in these men; 57% of men fully potent or with mild ED at baseline remained so 30 months after brachytherapy.

KEYWORDS

prostate cancer, therapy, sexuality, radiotherapy, brachytherapy

INTRODUCTION

In the absence of randomized trials showing that a particular treatment is better than another for localized prostate cancer (in terms of cause-specific survival) patients may value their quality of life as much as quality of life [1]. Urinary continence and erectile function (EF) are considered to be the most important determinants of quality of life after treatment for prostate cancer [1].

There is a wide range of reported potency rates after definitive therapeutic options for patients with localized prostate cancer. The reported potency after nerve-sparing prostatectomy is 20–90% when patients were followed long enough to account for the return of EF after surgery [2–4]. After external beam radiation therapy (EBRT), potency was preserved in 45–80% [5,6]. The results for preserving potency after permanent prostate brachytherapy are less forthcoming; in particular there is a paucity of prospective data using validated instruments [7,8].

To address this important issue we devised a prospective study by using the EF domain of the International Index of Erectile Function (IIEF questions 1–5 and 15) to investigate the effect of $^{103}$Pd brachytherapy on EF. In all, 78 consecutive patients with a follow-up of 30 months entered this study and completed the IIEF-15 at baseline and every 3 months thereafter.

PATIENTS AND METHODS

Between July 1999 and April 2003, 113 consecutive men with newly diagnosed localized prostate cancer were treated by permanent $^{103}$Pd seed implantation, with no EBRT, at our hospital. Inclusion criteria were clinical stages T1–T2, a PSA level of ≤15 ng/mL, Gleason score of ≤7 and a prostate volume of ≤50 mL (Table 1). Preoperative staging included TRUS of the prostate, pelvic CT and dynamic MRI of the prostate with an endorectal coil. In addition, a detailed medical history, including an assessment of factors with known effects on erectile dysfunction (ED), e.g. smoking habits, diabetes, hypertension and medication, was obtained. The partnership status was ascertained but more detailed information on this issue (e.g. partner interested in sexual activity, motivated partner, etc.) was not collected. For the current analysis, all 78 patients who completed a 30-month follow-up were analysed.

The $^{103}$Pd seeds were implanted under ultrasonographic guidance using an intraoperative computed planning template. $^{103}$Pd was used exclusively (half-life 17 days, initial dose rate 24 cGy/h, activity 51.8 MBq). From July 1999 to December 2000 a prescription dose of 115 Gy to the prostate,
maintaining a safety margin (3–5 mm) around the prostate, was delivered. From January 2001 to date, all patients received a prescription dose of 125 Gy according to the recommendations of the American Brachytherapy Society [9]. All procedures were performed by two physicians (A.R. and R.O.) in cooperation between the Department of Urology and Andrology and the Institute of Radio-oncology. The median (range) number of seeds implanted was 84 (45–122) and the number of needles used 37 (22–46). Post-planning after 1 month was standardized, revealing a median D90 (radiation dose delivered to 90% of the prostate target volume) of 112.8 (55.5–188) Gy.

To reduce the prostate, or as adjuvant treatment if the waiting time was >6 weeks, 65% of men received LHRH-antagonists, 5% antiandrogen monotherapy and 7% combined therapy for up to 3 months (all therapy started before 103Pd implantation, and no patient had therapy for >3 months). Only 23% of men were treated with no concomitant antiandrogen therapy. All baseline assessments (IIEF, quality-of-life score, PSA assay) were conducted before starting antiandrogen therapy.

To assess the effect of brachytherapy on EF and quality of life, the IIEF-15 questionnaire [10,11] and the EORTC QLQ C30 were completed before and every 3 months after brachytherapy by the patients. Questions 1–5 and 15 of the IIEF-15 were used as the EF domain score, and all patients had a routine oncological follow-up by a DRE, serum PSA assay, a measurement of postvoid residual volume and the IPSS at 3-month intervals; 78 men who reached the 30-month follow-up were analysed.

Differences in IIEF scores over time were calculated using the paired Student’s t-test and Wilcoxon signed-rank test. A multivariate regression analysis was used to identify independent factors predictive of preserved potency; in all tests, statistical significance was set at $P < 0.05$.

**RESULTS**

The baseline characteristics of all 113 patients treated within the study period, and of the 78 with a follow-up of 30 months who entered the present analysis, are shown in Table 1. Both groups were comparable in age, prostate volume, PSA and Gleason score. The distribution of men in the various categories of ED before brachytherapy is shown in Fig. 1; the median age for those with no, mild or moderate and severe was 68, 71 and 73 years, respectively. Table 2 compares the age, serum PSA level, prostate volume and comorbidity of the 27 fully potent men (IIEF >25) to the 51 with ED (IIEF <26) at baseline. Potent men were on average 4 years younger and had a lower incidence ($P < 0.05$) of diabetes mellitus.

Within the study population of 78 men there was a significant reduction of the mean IIEF score, from 43.2 before to 33.0 (−23.6%) 30 months after brachytherapy, and in the EF domain score, from 16.5 to 12.2 (−26.1%) (both $P < 0.001$) (Fig. 2). The IIEF and EF domain score improved slightly over time after a sharp decline 3 months after therapy.

Overall, 52 men (78%; including those with severe ED at baseline) remained in the same ED category as before therapy; 12 (15%) deteriorated by one category, 7 (9%) by two and a further 7 (9%) by three categories; no patient improved. The distribution of men in ED categories at baseline and 30 months is shown in Table 3; overall, 57% of patients with mild or no ED before treatment maintained that level 30 months afterward.

In a multivariate analysis, neither age nor preoperative PSA, prostate volume, D90, hormonal treatment, diabetes, smoking or hypertension were predictive factors for the
Discussion

Within the past decade prostate brachytherapy has become a popular definitive treatment option for localized prostate cancer. In the USA it is almost as common as radical prostatectomy, and is becoming increasingly popular in Europe. The preservation of potency is an important consideration for many (particularly young) men with localized prostate cancer when choosing among the three major definitive treatment options, i.e. radical prostatectomy, EBRT or brachytherapy. While the effect of radical (retropubic, perineal, laparoscopic) prostatectomy and EBRT on EF has been extensively assessed [2–6], data after brachytherapy are scant. To address this important issue several study prerequisites must be fulfilled, i.e. a prospective design, use of validated study instruments, an homogeneous study population and identical treatment, a reasonable sample size and sufficient follow-up. The present study meets these criteria and is, to our knowledge, the first prospective study exclusively using these criteria and is, to our knowledge, the first prospective study exclusively using brachytherapy with $^{103}$Pd, no EBRT and a validated questionnaire before and after treatment. To avoid any bias from different follow-up periods, only men who had 30 months of follow-up were included; patients with short-term survival therefore did not affect the data. This is particularly important for assessing ED after brachytherapy. The patient-administered IIEF used in the present study has been evaluated as a sensitive and specific tool for evaluating ED. Penson et al. [1] reported that physicians’ ratings of patients’ symptoms do not correlate well with patients’ self-assessment of quality of life, and reported significant differences between physician and patient assessment of all quality-of-life domains, including EF. Similar to the situation after radical prostatectomy or EBRT, a wide range of ED has been reported after permanent prostate brachytherapy as a result of 103Pd results in a decline in EF in about half of the men. The steep decrease in EF at 3–6 months after therapy, which recovers partly thereafter, is not only caused by 103Pd implantation but also by antiandrogen therapy. More important is that 57% of the men potent or with mild ED before therapy remained so 30 months afterward.

There was a high incidence of ED before brachytherapy in the present men; only 35% were fully potent at baseline, largely as a result of patient selection, underlined by a median age of 72 years at baseline. Younger men were treated by brachytherapy in our institution if they refused radical prostatectomy or if there was serious comorbidity. The present prospective data show that there was a high incidence of ED before brachytherapy in the present men; only 35% were fully potent at baseline, largely as a result of patient selection, underlined by a median age of 72 years at baseline. Younger men were treated by brachytherapy in our institution if they refused radical prostatectomy or if there was serious comorbidity.

Table 2

<table>
<thead>
<tr>
<th>Clinical variables and comorbidities of men with or without ED at baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
</tr>
<tr>
<td>PSA, ng/mL</td>
</tr>
<tr>
<td>Prostate volume, mL</td>
</tr>
</tbody>
</table>

Table 3

<table>
<thead>
<tr>
<th>The distribution of ED status according to EF score at baseline and after 30 months depending on the ED status at baseline, and the changes in the IIEF and EF score over time with initial ED category</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIEF score before</td>
</tr>
<tr>
<td>EF score before</td>
</tr>
</tbody>
</table>

Prostate brachytherapy and the mean EF (B) domain score with time. The bars indicate the SD (78 men).

Figure 2

Baseline 6 18 30
Time, months

Baseline 6 18 30
Time, months
available and is thus hampered as the IIEF score was not obtained before therapy. Valicenti et al. [13] assessed 34 men after \(^{125}\text{Pd}\) brachytherapy (with/without EBRT), reporting a 44% reduction in EF at 1 year after implantation. In that study the authors also analysed the role of short-term neoadjuvant endocrine therapy on the return of EF; there was no apparent long-term effect on EF, and no clear negative effect of neoadjuvant therapy in the short term [13]. Two other series with sufficient men but no validated questionnaires reported potency rates of 64% after 3 years in 313 men [14] and 76% after 5 years in a subgroup of men with no EBRT or androgen deprivation, from 482 patients [15].

ED after definitive local treatment for prostate cancer represents a multifactorial process, including neurogenic compromise, vascular insufficiency, local trauma and psychogenic causes. After radical prostatectomy, ED has been correlated with the surgical trauma to the neurovascular bundles, although potency rates even after nerve-sparing prostatectomy are unlikely to exceed 30–50% [16]. However, some series reported potency preservation rates of up to 90% after bilateral nerve-sparing prostatectomy, depending upon the erectile status before surgery, and age [17].

In contrast, after permanent prostate brachytherapy, the radiation dose to the neurovascular bundles does not correlate with the development of ED. However, there seems to be a strong correlation between the dose of radiation delivered to the bulb of the penis and the subsequent development of ED in EBRT. In addition, patient age, preoperative ED, supplemental EBRT, and the choice of isotope and antiandrogen therapy, may have a significant effect on the results. The continued documentation and elucidation of the causes of ED after permanent prostate brachytherapy, and advanced imaging of tumour location, may provide refined treatment techniques, lower rates of ED, and ultimately a better quality of life for the patients.

CONFLICT OF INTEREST
None declared.

REFERENCES

Correspondence: Robert Hawliczek, Chairman, Institute for Radiooncology, Donaustadion–SMZQ, Langobardenstrasse 122, 1220 Vienna, Austria. e-mail: hawliczek@smz.magwien.gv.at

Abbreviations: ED, erectile dysfunction; EF, erectile function; IIEF, International Index of Erectile Function; EBRT, external beam radiation therapy.
Comparison of laparoscopic and open donor nephrectomy: a randomized controlled trial

NASSER SIMFOROOSH, ABBAS BASIRI, ALI TABIBI, NASSER SHAKHSSALIM and SEYED M.M. HOSSEINI MOGHADDAM

Department of Urology and Renal Transplantation, Urology and Nephrology Research Center, Shahid Labbafi Nejad Hospital, Shahid Beheshti University of Medical Science, Tehran, Iran

Accepted for publication 15 November 2004

OBJECTIVE

To compare the graft survival, donor and recipient outcome, donor satisfaction, and complications of laparoscopic (LDN) and open donor nephrectomy (ODN) in kidney transplantation.

PATIENTS AND METHODS

In a randomized controlled trial, 100 cases each of LDN and ODN were compared. We modified the standard LDN procedure to make it less expensive.

RESULTS

The mean (±SD) operative duration was 152.2 (±33.9) min for ODN and 270.8 (±58.5) min for LDN, and the mean duration of kidney warm ischaemia was 1.87 min for ODN and 8.7 min for LDN. Only one LDN required conversion to ODN because of bleeding. The mean follow-up in the LDN and ODN groups was not significantly different (406.1 vs 403.8 days). The mean (±SD) score for donor satisfaction was 17.3 (±3.5) for ODN and 19.6 (±1.0) for LDN. The rate of ureteric complications was 2% for ODN and none for LDN. As determined by serum creatinine levels at 3, 21–30, 90, 180 and 365 days after surgery, graft function was not significantly different between ODN and LDN. Long-term graft survival was 93.8% for LDN and 92.7% for ODN.

CONCLUSIONS

Compared to ODN, LDN was associated with greater donor satisfaction, less morbidity and equivalent graft outcome.

KEYWORDS

laparoscopy, nephrectomy, kidney transplantation, living donor, randomized controlled trials

INTRODUCTION

Laparoscopic donor nephrectomy (LDN) was developed in an attempt to increase the frequency of kidney donation by reducing the disincentives to donation, capitalising on the associated reduced morbidity [1]. Ratner et al [2] reported the first successful human LDN in 1995. Later descriptive studies reported that the morbidity of LDN was less than with open DN (ODN) and that the long-term renal graft function of LDN was equivalent to that of ODN [2–4]. To our knowledge, the present study is the first randomized clinical trial comparing LDN and ODN. Preliminary results were reported previously [5].

Authors from Iran compare various outcomes between laparoscopic and open donor nephrectomy in kidney transplantation; they carried out a large comparative trial, and found that laparoscopic donor nephrectomy gave better donor satisfaction and morbidity, with equivalent graft outcome.
PATIENTS AND METHODS

The present prospective study began after gaining experience from 90 cases of LDN, and includes 100 cases of LDN and 100 of ODN performed between July 2001 and September 2003. Eligibility criteria were as follows: donor body mass index (BMI) <28 kg/m²; no complexity in the donor kidney vessels; recipient aged 18–65 years; and no haemolytic uraemic syndrome or focal segmental glomerulosclerosis and oxalosis in the recipient. All donors were evaluated at an outpatient visit 7–10 days after surgery. A telephone interview was conducted for donors at the closing date of study. The LDN or ODN was performed by two co-surgeons (68 ODN and 69 LDN by N.S. and 32 ODN and 31 LDN by A.B.) on the left kidney in all patients. The kidney was transplanted by the same urologist who did the nephrectomy.

The authors’ institution has adopted codes of ethics to guide human experimentation. After patients had been recruited and signed an informed consent form, they were assigned randomly to ODN and LDN groups, using a balanced randomization method [6].

The BMI was calculated; the warm ischaemia time was defined as the time from renal artery occlusion to kidney immersion in ice-slush, and operating time as the time from the initial skin incision to the final skin suture. Cold ischaemia time was defined as the time between kidney immersion in ice-slush and graft revascularization. Serial creatinine levels were measured in the recipient and recorded at 3 and 21–30 days, and 3, 6 and 12 months after transplantation. The definition of delayed graft function varies in different studies [7]; we defined delayed graft function as serum creatinine levels of >35 mg/dL on the third day after transplantation. Using a 20-point visual analogue scale (0 = no satisfaction to 20 = full satisfaction), we assessed donor satisfaction for discomfort and cosmetic result; the validity of this scaling method has not been assessed in previous studies.

All potential donors had an extensive medical and psychological evaluation, and received a light mechanical bowel preparation 12 h before surgery. Donors underwent conventional angiography or digital subtraction angiography to evaluate the anatomy of the kidney vasculature, and all donors with multiple renal arteries were excluded.

The surgical technique used for ODN was the standard retroperitoneal flank approach. For LDN, under general anaesthesia and using a transperitoneal approach in the modified flank position, a video laparoscope was introduced through a 12-mm umbilical port; 12-mm pararectal and 5-mm epigastric ports were used for the dissecting instruments. We used the following modifications to the conventional LDN: (i) the first trocar was introduced in an open technique using an ordinary non-disposable trocar (no Hasson’s trocar was used); (ii) we used three medium-large metal clips instead of an Endo-GIA stapler for ligating the renal veins and arteries; (iii) no organ-extracting device (e.g. Endo-catch bag) was used; the kidney was extracted manually via an 8–10 cm suprapubic incision.

The results were assessed statistically using Student’s t-test, nonparametric Mann–Whitney, Kaplan–Meier and chi-square tests as appropriate, with significance considered to be indicated at \( P < 0.05 \).

RESULTS

The patient demographics and surgical outcomes in the ODN and LDN groups are shown in Table 1. All nephrectomies were completed as scheduled, except for one LDN that required conversion to ODN because of bleeding. The mean (range) kidney warm ischaemia time was 1.87 (1–5) min for ODN and 8.7 (4–17) min for LDN (\( P < 0.001 \)). The mean interval between the beginning of surgery and cold washing of the kidney was 205 (123–320) min in the LDN and 89.13 (40–209) min in the ODN group (\( P < 0.001 \)), and the mean cold ischaemia time 48 (20–106) min and 49.4 (15–118) min, respectively.

No patients in the ODN group and only one in the LDN group required a blood transfusion.
during surgery. Two patients who had an ODN and one who had a LDN required re-operation. The reasons for re-operation were surgical site bleeding (one patient in each group) and pleural haemorrhage (one patient in the ODN group). There were no cases of malfunction of vascular clips on major vessels in the LDN group. Minor intraoperative complications are also shown in Table 1. A chest tube was inserted for all cases with intraoperative pneumothorax. The rate of postoperative donor complications was 17% in the LDN group and 9% in the ODN group (Table 1). There were no major complications in either group.

The mean (SD) score for donor satisfaction was 17.3 (3.5) for ODN and 19.6 (1.0) for LDN (P < 0.001). Eighty-five patients in the ODN group and 83 in the LDN group were discharged within 48 h of surgery. Table 2 shows the delay to resumption of ‘normal’ activities after LDN or ODN.

Three kidney recipients in the ODN group but none in the LDN group were donors’ first relatives. Two recipients in the LDN group and three recipients in the ODN group died, the reasons for death being given in Table 3. Long-term recipient survival was 96.9% in the ODN group and 97.9% in the LDN group (no significant difference; Wilcoxon statistic).

Ten recipients in the ODN and five in the LDN group had a history of previous kidney transplantation. The rate of recipient urological complications in the LDN and ODN groups was none and 6%, respectively. In the ODN group they included vein thrombosis in one patient (1%), stricture of the ureteric anastomosis in one (1%), lymphocele in two (2%), and both ureteric anastomosis leakage and lymphocele in one (1%). The rate of ureteric complications was none in the LDN group and 2% in the ODN group.

Delayed graft function was diagnosed in eight patients in the ODN and 11 in the LDN group. Within 3 months after transplantation, acute tubular necrosis was diagnosed in seven patients in the ODN and in 11 in the LDN group; and acute rejection in 11 in the ODN and in two in the LDN group. Graft function was not significantly different between the LDN and ODN groups, as determined by serum creatinine levels after surgery (Table 4). Long-term graft survival was 93.8% in the LDN and 92.7% in the ODN group. Three recipients in the ODN and two in the LDN group were lost to long-term follow-up.

**DISCUSSION**

Kuo et al. [8] reported that obese donors (BMI > 31 kg/m²) have similar outcomes with LDN as non-obese donors, but other studies have found that increasing patient weight correlates with longer operative duration [9]. To minimize the impact of obesity as an effect modifier, we narrowed the inclusion criteria of the present study to only include donors with a BMI of <28 kg/m².

Some researchers showed a halving in hospital stay for LDN and a more rapid return...
to work [1,10–12]. Lind et al. [3] stressed that LDN is associated with a shorter hospital stay than is ODN (2.2–2.7 vs 3.8–5.7 days). In our transplantation centre, the policy is to favour reducing the hospital stay, regardless of surgical technique. In the present study, the mean hospital stay in the LDN group was similar to that in other studies, but the mean hospital stay in the ODN group was shorter than in other reports.

Compared with ODN, LDN results in a shorter time until patients are able to drive, take care of the home, and return to full activity, work and regular exercise [11]. We divided the ordinary activities into ‘light activities’, ‘heavy activities’ and ‘ability for driving’. Donors in the LDN group had a significantly shorter delay to resuming each type of activity. Advantages of LDN thus include less loss of income and thus a lower financial burden for donors [13]. The cosmetic result of LDN is also better than that of ODN [14–16] and this seems to be important for the present patients’ reported satisfaction.

Using a 20-point visual analogue scale, there was significantly less reported pain in the LDN group, although the mean dose of parenteral analgesia delivered after surgery was lower. Reasons for the differences were: (1) the use of a controlled analgesia system and LDN was managed after surgery with a patient-controlled analgesia system and LDN was associated with less postoperative pain and a lower analgesic requirement.

The present study showed that warm ischaemia time (within the range of our data) did not significantly affect graft function. Buondon et al. [18] reported on 640 LDNs and found no effect of warm ischaemia time on recipient graft function within the range of 35–720 s. In the present study the longest time of warm ischaemia was 1020 s, longer than that recommended as a safe limit by Buondon et al. [18]. Warm ischaemia time (within the present range) had no correlation with recipient serum creatinine levels at the measured intervals, suggesting that any damage from warm ischaemia might be reversible.

In the present study, there was no significant difference in postoperative complications between the groups. Donor complications in the LDN group seem to be declining, and with increasing experience should be less common. In previous studies, the conversion rate from LDN to ODN was 1.6–13% [11,19], but such conversion was required in only one patient in the present study.

There is a different pattern of complications and morbidity in ODN. Although one report [10] showed that ODN has a higher incidence of pneumothorax, flank nerve entrapment and flank hernia, in the present study one patient in each of the groups had thigh numbness which might be a result of nerve entrapment in the flank. Patients in both the present groups had no major intraoperative complications. In a recent series from the University of Maryland [19] among 738 LDNs 15 major complications, including 13 vascular injuries and two bowel injuries, were reported. In the present study, two patients who had an ODN and one who had LDN required reoperation.

In the present study, recipients after LDN had no ureteric complications. We performed a wide dissection around the ureter, maintaining adequate peri-ureteric fat; this wide dissection might explain the relatively low incidence of recipient ureteric complications. We also had no complications from trocar entry; this success probably reflects the policy of simple open access, whereby we introduced a regular reusable trocar from a 1.5-cm incision above the umbilicus (a modification of Hasson’s technique). The success of this LDN modification lowers the financial burden upon donors, which might be particularly important for donors in developing countries. Further efforts should be made to simplify laparoscopic instrumentation and lower the cost of surgical instruments used for LDN.

LDN seems to be an attractive alternative to ODN. Our modification to LDN is technically feasible and, compared to ODN, gives greater donor satisfaction, a faster return to work and ordinary activities, and less pain after surgery. Kidneys harvested by LDN have equivalent function to those harvested by ODN, graft survival is similar with the two approaches, and the warm ischaemia time (within the range of our data) appears to be safe.

**CONFLICT OF INTEREST**

None declared. Source of funding: Urology Nephrology Research Center (UNRC).

**REFERENCES**


13. Ratner LE, Kavoussi LR, Sroka M et al. Laparoscopic assisted live donor...
nephrectomy: a comparison with the open approach. Transplantation 1997; 63: 229–33

Correspondence: Nasser Simforoosh, Urology Nephrology Research Centre, Shahid Labbafinejad Hospital, Boostan 9th St., Pasdaran Ave, PO Box 1666679951, Tehran, Iran.

Email: simforoosh@iurtc.org.ir

Abbreviations: L(O)DN, laparoscopic (open) donor nephrectomy; BMI, body mass index.
Reconstructive Urology

Determinaton of the time required for appropriate chemical de-epithelialization of an ileal segment for cystoplasty: an animal model

JALAL BAKHTIARI, HAMID REZA FATTAHIAN, MOHAMMAD JAVAD GHRAGOZLOU*, ABDOLMOHAMMAD KAJBAFZADEH† and SEYED REZA JAFARZADEH Departements of Clinical Sciences and *Pathobiology, Faculty of Veterinary Medicine, University of Tehran, and †Department of Paediatric Urology, Children's Hospital Medical Center, Tehran University of Medical Sciences, Tehran, Iran

Accepted for publication 12 November 2004

OBJECTIVES

To determine the time required for the appropriate enzymatic treatment of an ileal segment to de-epithelialize its mucosa and to reduce its absorptive function for cystoplasty in dogs.

MATERIALS AND METHODS

Twenty-one adult female Persian mixed-breed dogs were divided into seven equal groups: group 1 (negative control group) had no ileocystoplasty; group 2 (positive control group) had a routine ileocystoplasty with no enzymatic treatment of the ileal segment; and groups 3–7 had an ileocystoplasty with 5, 10, 15, 20 or 25 min, respectively, of enzymatic treatment of the ileal segment with collagenase and trypsin. The seven groups were then compared for haematological, biochemical and histological changes, and glucose reabsorption assessed using a glucose-absorption test.

RESULTS

No dogs showed any signs of metabolic disturbances, biochemical and haematological changes. There were significant differences in blood glucose level (BGL) for the groups at different times after the glucose-absorption test, but a pair-wise comparison showed significant differences in BGL between group 1 and the other groups, except group 7. The degree of histopathological change was associated with the duration of enzymatic treatment, in that changes were more prominent in group 7. There was no shrinkage or collagen deposition.

CONCLUSIONS

In these conditions, 25 min of enzymatic treatment of the ileal segment is sufficient to remove the absorptive function of the augmented bladder, and is recommended for cystoplasty in dogs.

KEYWORDS
de-epithelialization, cystoplasty, enzymatic treatment, glucose absorption test, dog

INTRODUCTION

Ileocystoplasty is used often to reconstruct the bladder in patients with end-stage bladder dysfunction when other more...
conservative management fails. Almost all parts of the gastrointestinal system have been successfully incorporated into the urinary bladder for urinary diversion, to increase capacity, improve compliance, or abate uncontrollable detrusor contractility, and for intractable interstitial cystitis [1–5]. Complications include the metabolic disturbances secondary to electrolyte reabsorption, metabolic acidosis because of the absorptive function of epithelial tissue on the ileal segment, asymptomatic chronic bacteriuria, UTIs, vitamin B deficiencies in children, urinary obstruction secondary to mucus formations of goblet cells, diarhoea after neural stretch reflexes, osteomalacia and osteopenic changes, adenocarcinoma, bladder rupture after ischaemia or scar tissue formation along the anastomosis, which may question the beneficial effects of the procedure [6]. Several techniques have been introduced for mechanical gastrointestinal mucosal ablation, with different clinical results [6]. Enzymatic treatment of the ileal segment has been suggested for de-epithelialization of its mucosa and reducing its absorptive and secretive functions [7]. Thus the purpose of the present study was to determine the required time for appropriate enzymatic de-epithelialization of an ileal segment for cystoplasty.

MATERIALS AND METHODS

The study included 21 female Persian mixed-breed dogs (aged 1–2 years, 15–24 kg), vaccinated and prescribed anti-helminth agents before surgery. The dogs were given neomycin sulphate (0.5 mg/kg, orally) for 24 h and were fasted for 12 h before surgery. The dogs were divided into seven equal groups (randomly assigned): in group 1 (negative control group) the dogs had sham surgery with no ileocystoplasty; in group 2 the dogs had a routine ileocystoplasty with no enzymatic treatment of the ileal segment; in groups 3–7 the dogs had an ileocystoplasty with an ileal segment treated for 5, 10, 15, 20 or 25 min, respectively, with 100 mL of a 0.125% enzymatic cocktail, consisting of collagenase and trypsin.

For the surgical procedure, an intravenous line was started beforehand and all dogs received 5% dextrose-lactate-Ringer’s solution at 60 mL/kg. Cefazolin (20 mg/kg, intravenous) was administered as a prophylactic antibiotic before inducing anaesthesia. The anaesthetic protocol was by atropine sulphate (0.02 mg/kg, subcutaneous) as premedication, and diazepam (0.27 mg/kg) and ketamine hydrochloride (5.5 mg/kg, both intravenous) to induce, and 1% halothane to maintain, anaesthesia. After the abdominal skin was shaved and disinfected with povidone–iodine, the surgery was through a midline incision. A 20-cm long ileal segment at least 10 cm proximal to the ileocaecal valve and before the ileocaecal ligament, with an adequate mesentery to reach the native bladder, was selected. The mesentery was cleared from the bowel at each end for a short distance to create a window, and the bowel divided at these ends. Intestinal continuity was re-established with an ileo–ileostomy created using an end-to-end anastomosis with a single-layer simple interrupted 3–0 polyglactin 910 suture. The ileal segment for augmentation was irrigated clear with 0.9% normal saline and 0.25% neomycin sulphate solution. The ileal segment was treated enzymatically according to the predetermined time, and +5 mm of the ileal segment surgically resected and assessed to determine the degree and extent of enzymatic effects on the intestinal epithelium. The intestinal segment ends, which were clamped during the enzymatic treatment, were cut to ensure equal enzyme contact throughout the segment. Then 15 cm of the ileal segment was opened on its antimesenteric border, detubularized and reconstructed as a U shape. The bladder was then incised in the sagittal plane, extending near the bladder neck ventrally and near the trigone dorsally. The ileal segment was the anastomosed to the native bladder using a two-layer closure (an inner layer of running 3–0 polyglactin 910 and an outer layer of running Cushing 3–0 polyglactin 910). The mesenteric window at the bowel anastomosis was closed. The water-tightness of the ileo–ileostomy and ileocystoplasty were checked by injecting 0.9% normal saline solution into the augmented bladder, to detect any leakage from the suture lines. The abdominal cavity was irrigated with 0.9% normal saline solution. The peritoneum and abdominal muscles, and subcutaneous layers were separately closed with a single-layer of running 3–0 polyglactin 910 suture, and the skin closed with simple interrupted 3–0 polyamide sutures. The skin was bandaged to prevent self-mutilation and contamination. After surgery all dogs received intravenous fluids for 24 h and cefazolin (20 mg/kg, intramuscular for 8 h) for 3 days.

Blood samples were drawn from the cephalic vein at 0, 14 and 35 days to assess haematological and biochemical changes, and ultrasonography used at 14 and 35 days to evaluate the augmented bladder wall thickness. The absorptive capacity of the ileal segment epithelium was determined using a glucose absorption test; 5 weeks after surgery, 60 mL of 50% dextrose was instilled through a 12 F Foley catheter into the bladder. The blood glucose level (BGL) was then measured in each group before anaesthesia (T1), after anaesthesia to assess glucose absorption (T2) and at 5-min intervals for up to 25 min (T3 to T7, respectively).

Epithelial loss, as assessed on histopathological sections on the day of surgery, was graded on a scale of +1 to +4, representing ≤25% 25–50% 50–75% and 75–100% loss of epithelium, respectively. The histology of the augmented bladder was assessed at the end of the follow-up. After anaesthesia, the abdomen was re-opened and the general aspect of the augmented bladder and vascularization of the graft evaluated, with special attention to appearance, texture and elasticity. The augmented bladder was removed, opened, fixed in 10% buffered formalin and embedded in paraffin wax. Random histological sections of 5 μm thick were stained with haematoxylin and eosin (H&E) and Masson’s trichrome. Animals were killed 35 days after surgery with an overdose (intravenous) injection of thiopental sodium solution. All layers in the bladder, the ileal segment and in the vesico-enteric junction were evaluated by light microscopy.

A mixed-model (repeated-measures) ANOVA was used to compare BGL among the groups and within each group at different times (T1–T7), with P < 0.05 considered to indicate significance [8,9].

RESULTS

There was no difference in serum electrolytes, blood urea nitrogen, creatinine, total protein, albumin, blood gases, triglycerides, cholesterol, anion gap and haematological profiles in all groups. Ultrasonography showed a mean wall thickness of 2.30 mm in the ileal segment, 2.41 mm in the native
There were significant differences in BGL among the groups and at different times; pair-wise comparison showed significant differences in BGL between group 1 and the other groups, except group 7, which indicated that the acceptable enzymatic treatment time was 25 min (i.e. in groups 1 and 7 there was a similar amount of glucose absorbed via the bladder). Although the BGL was lower in group 6 than 2–5, it was not statistically significant, indicating that 20 min of enzymatic treatment of the ileal segment was not enough to completely abolish the absorptive capacity of the bladder to a level similar to that in group 1, as occurred in group 7 (Fig. 1). The pair-wise comparison also showed significant differences in BGL in T1 or T2 with the other times (T3–T7).

Histological sections taken on the day of surgery showed that 5 min of treatment denuded focally 20% of the villi epithelium (+1) while 10 min caused 33% denudation of the villi epithelium (+2) with partial crypt lysis. At 15 min of treatment about half the villi were de-epithelialized (+2) while 20 min caused 75% denudation (+3) with more crypt lysis, and almost complete denudation of villi epithelium (+4) at 25 min. The lamina propria, stratum compactum, Peyee’s patches, muscular layers and serosa were intact in all sections except those treated for 25 min. Mild vascular damage, petechial haemorrhage in the villi apex and villi separation were apparent in a few histopathological sections.

Macrosopically, the adventitia, the mesenteric vasculature, smooth muscle layers, transitional and ileal mucosa were normal in appearance. The internal surface of the augmented bladder was completely covered with apparently healthy mucosa. Compared with other parts of the bladder, the vesico-enteric junction was uniformly thickened and elevated.

The native bladder tissues, including transitional cell layer, submucosal, muscle layers and adventitia, were normal in appearance but in some cases there was a mild to moderate oedema of the submucosal connective tissues.

In the vesico-enteric junction, the histopathology showed transitional cell hyperplasia, metaplasia and transitional epithelium growing and migrating over the intestinal villi, which formed a urothelial-like layer over the intestinal epithelium (urothelialized to the top of the villi). There was fairly mature granulation tissue and fibrosis, and focal and diffuse infiltration of lymphocytes at the junctional zone.

On Masson’s trichrome staining a few smooth muscle fibres were found within the healing mature granulation tissues at the junctional zone (Fig. 2). Heterotopic bone formation was found in the vesico-enteric junction in two of 18 dogs, and in one there was a mucocele lined by attenuated epithelial cells, containing mucus material and desquamated cells.

In the ileal segment, the smooth muscle layers, myenteric plexus, Peyee’s patches and serosa of the ileal tissue were intact. The mucosa showed atrophic changes characterized by blunting and a reduction in both villus height and crypt depth. In some animals the atrophic changes were very marked, in which the crypts were absent and the villi originated from the vicinity of the muscularis mucosa. Some villi showed severe atrophic changes, appeared as very narrow filiform villi composed of two layers of adjacent modified epithelial cells, with no discernible lamina propria. There were fewer goblet cells. The intervilli space was wider, and in some animals the crypts were dilated and contained a mixture of mucus and proteaceous eosinophilic material. At the sites of the enzymatic interactions where the epithelial cells of villi had been lysed and desquamated, the lost epithelial cells were...
replaced by hyperplastic, attenuated, deformed regenerated uniform cells which, in contrast to the normal epithelial cells of the villi, had the long axis of their nuclei parallel to the basement membrane. In addition there were no goblet cells among the regenerated epithelial cells (Fig. 4). Collagen deposition (fibrosis) was not seen in all groups (Masson’s trichrome staining).

The histopathological changes seen in all the experimental groups were relatively constant, but the degree of change was associated with the duration of enzymatic treatment, so that the changes were more prominent in group 7. There was no necrosis, dysplastic changes, granulomatous reactions and fibrosis or any undesirable tissue alterations in the augmented bladder.

DISCUSSION

Gastrointestinal segments are a very useful source for reconstructing and augmenting the urinary bladder in the management of various problems. Unfortunately, no intestinal segment is a physiological substitute for the native bladder. The complications of augmentation cystoplasty may persist and are significant for some patients [6]. The magnitude of the complications depends on the type of intestinal segment used, the amount of functional mucosa, the duration of the contact of urine with epithelium, and renal functional capacity [10,11]. There are many suggestions for de-epithelializing the intestinal mucosa, and reducing its absorptive and secretive functions, to fulfill the requirement of an ideal substitute, including mechanical, seromuscular enterocystoplasty, chemical destruction of the intestinal mucosa by hypertonic normal saline solution, hemi-acidrin, photochemical ablation using haematoporphyrin derivatives and red light, collagenase and trypsin, protamine sulphate and urea solution, silver nitrate solution and HEPES-buffered saline [6,12–16].

The absence of significant changes in the biochemical data reflects the absence of renal damage and significant metabolic disturbances secondary to bladder and intestinal surgery [14]. We found that 25 min of enzymatic treatment could completely de-epithelialize ileal mucosa. One study showed that >90% of the epithelium was removed when bladders were treated using protease at 10 mg/mL and urea at 200 g/L for 15 min in a volume of 50–60 mL [14].

In the present study, except for mild to moderate oedema in some cases, all layers of native bladder were of normal appearance. A urothelium-like layer of migrating transitional epithelium, with hyperplasia and metaplasia, was evident on top of the intestinal villi, as previously seen in rats [17]. The few smooth muscle fibres apparent within the healing mature granulation tissues at the junctional zone may originate from the muscularis layers of the native bladder or ileal segment. It was stated that they are the result of hypertrophy, migration and differentiation from connective tissue cells [18,19]. In two cases, heterotopic bone formation was apparent in the vesico-enteric junction, which was previously seen at the junctional zone of bladder and bovine amniotic membrane [20].

In the present study, enzymatic treatment had no significant adverse effects on the ileal layers, consistent with other studies [7]. The atrophic changes consisting of reduced villous height and crypt depth were also documented by some [21] although others reported increases in height and crypt length, or markedly reduced height of villi with normal crypt depth in a rat model [22,23]. In the present model there were also severe atrophic changes of villi which gave them a narrow filiform appearance.

Enzymatic treatment of an ileal segment by collagenase and trypsin was previously successful in rats [7]; the epithelium was atrophied in the control and treatment groups, and it completely abolished the absorptive function of the epithelium, while the BGL increased to twice the baseline values in the control group.

In the present model, glucose was gradually absorbed from the bladder with autotransplanted ileum, but the absorption rate of the augmented bladder using a standard ileocystoplasty procedure was rapid. The malabsorption of an intestinal segment used as the urinary bladder seems to be favourable, because hyperchloric acidosis caused by urine reabsorption cannot occur. However, studies show that carbohydrate absorption is not generally impaired [24].

There was no statistically significant difference in BGL between groups 1 and 7, indicating that enzymatic treatment for 25 min was sufficient; both groups 1 and 7 absorbed a similar amount of glucose via the bladder, showing that 25 min of enzymatic treatment can reduce the absorptive capacity of an ileal segment to that of a normal bladder. Enzymatic treatment for 20 min was insufficient to properly abolish the absorptive capacity of the bladder to a level similar to that in groups 1 and 7. This confirms that 25 min of enzymatic treatment of the ileal segment for ileocystoplasty is enough to remove the absorptive capacity of the bladder, and not increase the BGL for up to 25 min after glucose absorption in dogs. A shorter duration (5–20 min) of enzymatic treatment did not significantly reduce the absorptive function of the bladder.

Glucose is basically transported through the intestinal membrane in a co-transport mode with the active transport of sodium. In the first stage, sodium is actively transported through the basolateral membranes of the intestinal epithelial cells into the paracellular spaces. In the second stage, sodium combines with a transport protein in the interior of the cell, but this protein does not transport the sodium until it also combines with some other appropriate substances, e.g. glucose [24]. Normal bladder has neither absorptive nor secretive ability [23]. The reduction of
absorptive function of an enzymatically treated ileal segment was probably a result of changes in the ultrastructure of cellular membranes [7]. Although the present study showed that glucose absorption through the ileal membrane was abolished after 25 min of enzymatic treatment, some extrapolation is possible for the associated electrolyte movements.

**ACKNOWLEDGEMENTS**

The authors thank Drs Iraqj Nowrouzian, Abbas Veskhini and Dariush Shirani for their kind assistance during the study. This study was supported by the Research Council, University of Tehran (Grant # 218/3/512).

**CONFLICT OF INTEREST**

None declared. Source of funding: Research Council, University of Tehran (Grant 218/3/512).

**REFERENCES**

16. Liu U, Lee AM, Terris MK. Effectiveness of denuding the intestinal mucosa by submucosal injection in the porcine model. *Tech Urol* 2001; 7: 70–4

**Correspondence:** Jalal Bakhtiari, Department of Clinical Sciences, Faculty of Veterinary Medicine, University of Tehran, PO Box 14155-6453, Tehran, Iran. e-mail: bakhtiari@doctor.com

**Abbreviations:** H&E, haematoxylin and eosin; BGL, blood glucose level.
The laparoscopic management of intersex patients: the preferred approach

FRANCISCO T. DÉNES, MARCELO A.S. COCUZZA, EDISON D. SCHNEIDER-MONTEIRO, FREDERICO A.Q. SILVA, ELAINE M.F. COSTA*, BERENICE B. MENDONÇA* and SAMI ARAP

Divisions of Urology and *Clinical Medicine and Endocrinology, University of São Paulo School of Medicine Hospital, São Paulo, Brazil

Accepted for publication 30 November 2004

OBJECTIVE

To present possibly the largest series of the use of laparoscopy for treating intersex patients.

PATIENTS AND METHODS

Fifty intersex patients (34 with male and two with female pseudohermaphroditism, nine with gonadal dysgenesis, four with true hermaphroditism, and one with complex hypospadias), aged 0.5–46 years (mean 18.3), underwent laparoscopy to remove gonads and/or ductal structures incompatible with the social gender, or for gonadal tumour or a potential risk for malignancy. When necessary, genitoplasty was performed concomitantly.

RESULTS

At the laparoscopic evaluation, 10 gonads of six patients were absent, while four were identified as ‘vanishing’; 72 gonads (46 dysgenetic, 17 normal testes, one normal ovary, one ovotestis, seven gonadoblastomas or dysgerminomas) were removed; two ovotestes were replaced in the scrotum after removing the ovarian segment, as was one normal testis. Twelve patients with a urogenital sinus had its vaginal component removed, 11 including a hysterectomy. Three of these patients had a combined perineal approach to complete its removal, together with masculinizing genitoplasty. There were no intraoperative complications or conversions; two patients had complications after surgery.

CONCLUSIONS

Laparoscopy allows the straightforward identification and removal of gonads. All abnormal ductal structures must be removed, as this increases the chance of resecting unidentified gonads. Removing the uterus and vaginal component of the urogenital sinus in patients with male social sex is feasible, with low morbidity. Genitoplasty, according to the social sex, can be performed in the same procedure.

KEYWORDS

intersex, laparoscopy, treatment, gonads, ovary

INTRODUCTION

The management of patients with intersexual states is clinically demanding. Only with a careful clinical evaluation can the correct diagnosis be established, therefore reducing the probability of therapeutic misconduct (mainly for sex assignment). The therapeutic
PATIENTS AND METHODS

From March 1994 to April 2004, 50 patients with intersex disorders (mean age 18.3 years, range 0.5–46) were treated at our institution. The disorders included male pseudohermaphroditism (MPH) in 34 patients, female pseudohermaphroditism (FPH) in two, mixed gonadal dysgenesis (GD) in nine, true hermaphroditism (TH) in four and complex hypospadias in one. Laparoscopy was indicated for evaluation, but mainly to remove unwanted gonads and ductal structures. Whenever necessary, associated genitoplasty was also performed.

The preoperative evaluation included a careful clinical history and detailed physical examination, particularly of the external genitals and perineal orifices, with palpation of the inguinal area [1]. Hormonal, cytogenetic and radiological investigation (pelvic ultrasonography and retrograde genitography) were also used.

The patients had a general anaesthetic with endotracheal and nasogastric intubation. The patients had a general anaesthetic with endotracheal and nasogastric intubation. The surgical technique included the classical steps for laparoscopic surgery, i.e. peritoneal insufflation with a Veress needle inserted infraumbilically, insertion of a 5–10 mm umbilical trocar for laparoscopic evaluation, and two or three additional pelvic trocars for therapeutic procedures. The patient was then placed in a Trendelenburg position. The gonadal structures were evaluated initially, and when necessary, the bowel retracted. In some cases when the gonads are not easily seen, the gonadal vessels may be identified and followed downwards. Most often, the gonads are identified near the inguinal region, eventually with normal testicular or ovarian appearance, but also with a dysplastic or tumoral aspect. In some cases the gonads are not clearly identified because of dysplasia, sometimes leading to confusion with ductal structures. Once identified, the gonads are resected, most often together with the ductal structures. In the presence of a normal testis in a patient with a male social sex, laparoscopic orchidectomy can be performed [2].

MPH represents the most frequent indication for therapeutic laparoscopy [1]. As the patient with an underdeveloped phallus is generally orientated to the female gender, the testes must be resected. When present, the hypoplastic uterus should be left, to allow the possibility of menstruation and pregnancy [4,5]. When the testes are palpable, orchidectomy can be done through inguinotomies, but as most such patients have impalpable testes, a laparoscopic orchidectomy is indicated [6,7]. When the patient is assigned to or assumes a male role, laparoscopic gonadectomy is still necessary when the gonads are dysgenetic or tumoral, but when the testes are normal, orchidectomy is indicated. In cases of MPH with male gender, resection of Müllerian duct derivatives is always necessary [8]. In the rare cases of FPH with a male social sex, laparoscopic orchidectomy or resection of testicular tissue from the ovotestis is indicated. In patients with TH and male social sex, laparoscopic orchidectomy or resection of testicular tissue from the ovotestis is indicated. In patients with TH and female social sex, laparoscopic orchidectomy or resection of Müllerian duct derivatives, ovary or the ovarian tissue from ovotestis is indicated, as well as orchidectomy in selected cases. In patients with

### TABLE 1 Guidelines for the laparoscopic management of the gonads and Müllerian derivatives in intersex patients

<table>
<thead>
<tr>
<th>Clinical intersex diagnoses</th>
<th>Possible findings</th>
<th>Social sex</th>
<th>Laparoscopic management</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPH</td>
<td>Normal gonads, MDD</td>
<td>Male</td>
<td>Gonadectomy resection of MDD</td>
</tr>
<tr>
<td>MPH</td>
<td>Normal gonads and/or dysgenetic gonads; MDD</td>
<td>Female</td>
<td>Gonadectomy (when dysgenetic)/orchidopexy (when normal) Resection of MDD</td>
</tr>
<tr>
<td>TH</td>
<td>Normal gonads, ovotestis MDD</td>
<td>Female</td>
<td>Orchidectomy/resection of testicular tissue from ovotestis Resection of ovarian tissue from ovotestis/orchidopexy Resection of MDD</td>
</tr>
<tr>
<td>GD</td>
<td>Dysgenetic gonads, MDD</td>
<td>Female</td>
<td>Gonadectomy (Y chromosome)</td>
</tr>
</tbody>
</table>

MDD, Müllerian duct derivatives.
GD, particularly those with a Y chromosome, gonadectomy is essential, while resection of Müllerian duct derivatives is indicated in patients with male social sex [8].

Because of social and geographical conditions, most of the present patients were first evaluated as adults, and their treatment adjusted to the already defined sexual role.

The laparoscopic procedures, according to clinical diagnosis, social sex and laparoscopic findings, are summarized in Table 1. When necessary, associated genitoplasty is also performed, according to the sexual role of each patient.

We evaluated the efficacy of laparoscopy in identifying the gonads, the success of gonadal and ductal resection, the relationship between surgical findings and gonadal histology, the need for conversion to an open procedure, the incidence of complications during or after surgery, and the need for blood transfusion.

RESULTS

All 50 patients had a laparoscopic evaluation that identified the pelvic structures. Ten gonads in six patients were absent on laparoscopic evaluation. Two patients had bilateral ‘vanishing testes’ identified by blind-ending gonadal vessels. We defined laparoscopically 86 structures as gonads; some of these were not confirmed histologically, as described below.

The ductal structures were also very variable, ranging from normal epididymis and Fallopian tubes to vestigial structures associated or not with normal or hypoplastic uteri. Differences were also noted between sides in the same patient. In all, 17 uteri and 12 urogenital sinuses were confirmed laparoscopically.

After laparoscopic evaluation there were 38 bilateral and seven unilateral procedures intended to remove gonads and ductal structures, as well as 12 resections of the vaginal component of the urogenital sinus, six hysterosalpingectomies and five hysterectomies, one unilateral orchidectomy, and one resection of an ovarian segment of ovotestis associated with orchidectomy [Fig. 1]. One bilateral herniorrhaphy and one cholecystectomy were also performed.

Only 75 gonads were confirmed histologically, including five that were not identified during surgery, but were resected incidentally together with the ductal structures. These gonads were either normal but contrary to the social sex, dysgenetic or tumoral.

Three of the 12 patients with a urogenital sinus who had its vaginal component removed laparoscopically required a combined perineal approach to complete the removal, which was accomplished together with masculinizing genitoplasty. Associated genital masculinization was done in 12 patients and feminization in seven. One ovotestis was replaced without laparoscopy in the scrotum after removing the ovarian segment.

Five patients had seven neoplastic gonads (represented mainly by gonadoblastoma, a tumour of low malignant potential, and dysgerminoma, a malignant tumour), but only three of these gonads were enlarged (as seen before surgery on imaging, and during laparoscopy), suggesting tumoral involvement (Fig. 2) (Table 2).
All procedures were completed with minimal blood loss, except in one patient who had significant bleeding during genitoplasty, receiving one unit of blood. The duration of the procedures was 55–270 min, including associated genitoplasty. There were no complications during surgery nor conversion to laparotomy, but in one patient with TH the resection of the ovarian portion of the ovotestis and subsequent orchidopexy was done through an inguinal incision, after laparoscopic removal of the uterus and urogenital sinus, and the contralateral gonad. Only two patients had complications after surgery, one with an umbilical port infection and another with a pelvic abscess, both successfully treated with antibiotics. When there was only a laparoscopic procedure the hospital stay was 1–3 days, and with associated genitoplasty the stay was 6–11 days.

DISCUSSION

The first laparoscopic bilateral gonadectomy in an intersex patient was reported in 1992 and since then this procedure has gradually become the standard for evaluating and treating the internal genital organs in these patients [9,10]. The classical advantages of laparoscopy include the elimination of a sizeable laparotomy incision, resulting in less discomfort after surgery, less need for analgesia, and a shorter hospital stay, convalescence and return to normal activities [10]. Other advantages include magnification, excellent visibility and illumination, and less venous oozing because of the pressure effect of the pneumoperitoneum. One of the main advantages of this method is the lack of scars, a very important issue for these patients, who need reaffirmation of their body image and self-esteem [1].

The intersexual states for which laparoscopy is more frequently used are MHP, FHP, TH and GD [1]. It is helpful for gonadal evaluation, resection or biopsy, and for identifying internal ductal derivatives [3,11]. It is also used for removing all normal structures contrary to the assigned social sex, as well as gonads that are either dysgenetic, nonfunctional or malignant or of increased malignant potential [12,13].

Laparoscopy gives an excellent view of the pelvic structures, including the genital organs. In most cases identifying these structures is easy and their removal straightforward. However, the accuracy of identifying the gonads is not total. As documented here, there are cases where structures identified as gonads and removed were not confirmed histologically as such. On the other hand, some dysgenetic gonads were not identified, being removed incidentally as ductal structures. This reinforces the need to remove all ductal structures when the gonads are not clearly identified, as most unseem dysplastic and potentially malignant gonads will be thus removed.

The relative risk for testicular germ-cell tumours associated with intersex syndromes is increased more than 100 times, justifying prophylactic gonadectomy as soon as is feasible after the diagnosis is established [14]. The risk of gonadal neoplasia is not confined to patients with a 46,XY karyotype, but extends to patients with GD and any mosaic karyotype containing a Y chromosome or the SRY antigen [15]. In the present patients 9.3% of the gonads in 10% of the patients had tumours, but only three of them had macroscopic abnormalities suggesting tumour.

We treated all patients by laparoscopy, with no conversion to laparotomy, or significant bleeding or intraoperative complications. The most difficult procedures are those associated with resecting the vaginal portion of the urogenital sinus, particularly in those whose distal end extends beyond the urogenital diaphragm. The complication rate after surgery was 4%, including two localized infections treated successfully with conservative measures.

In conclusion, laparoscopy allows easy visualization of impalpable gonads, ductal remnants and urogenital sinus in intersex patients. All procedures necessary for adequately treating intersex disorders can be done with few complications and all the advantages of the laparoscopic procedures, even in small children. All dysgenetic, nonfunctioning and neoplastic gonads, and contradictory ductal structures, can be resected. In cases where the gonad is not clearly identified, ipsilateral ductal derivatives must be resected, as some specimens may include undetected dysgenetic gonads. Laparoscopic resection of urogenital sinus, with or without the uterus, is feasible. Complementary perineal resection of the inferior vaginal segment of the urogenital sinus may be required. Genitoplasty, according to social sex, can be performed simultaneously with laparoscopy.

CONFLICT OF INTEREST

None declared.

REFERENCES

11. Major T, Borsos A, Csiszár P.


Correspondence: Francisco T. Dénes, Division of Urology, University of São Paulo School of Medicine Hospital, Caixa Postal 11273–9, CEP 05422–970, São Paulo, SP, Brazil.
e-mail: f.c.denes@br2001.com.br

Abbreviations: MPH, male pseudohermaphroditism; FPH, female pseudohermaphroditism; GD, mixed gonadal dysgenesis; TH, true hermaphroditism.
Predictive factors of ultrasonographic involution of prenatally detected multicystic dysplastic kidney

ELI ARMANDO S. RABELO*, EDUARDO A. OLIVEIRA†, GUILHERME SOUZA SILVA*, ISABELA LEITE PEZZUTI* and EDSON SAMESINA TATSUO‡
*Paediatric Nephrourology Unit, †Department of Paediatrics, and ‡Department of Surgery, Hospital das Clínicas, Federal University of Minas Gerais – Belo Horizonte, MG, Brazil

Accepted for publication 15 November 2004

OBJECTIVE
To evaluate possible predictive factors of involution on ultrasonography (US) or disappearance of a prenatally detected multicystic dysplastic kidney (MCDK).

PATIENTS AND METHODS
Forty-five children with unilateral MCDK detected by prenatal ultrasonography between 1989 and 2002 were analysed. All patients except one had 99mTc isotopic scintigraphy to confirm the absence of renal function in the MCDK. All children were managed conservatively with follow-up visits every 6 months, with US 6-monthly during the first 2 years of life and yearly thereafter. Survival was analysed using the Kaplan-Meier method to evaluate the involution of the MCDK, with differences between subgroups assessed using the two-sided log-rank test. Cox’s regression model was applied for the multivariate analysis.

RESULTS
The mean (range) follow-up was 50 (12–167) months; in all, 279 ultrasonograms were taken, the mean (range) number per patient being 6 (3–10). US showed partial involution of the MCDK in 30 (67%) cases and complete involution in nine (20%). The absolute MCDK length remained almost unchanged in six children (13%). Univariate analysis showed that four variables were possibly associated with complete involution of the MCDK (gender, palpable kidney, renal length at admission using two thresholds, 62 and 78 mm). After adjusting by Cox’s model only a renal length at diagnosis of <62 mm remained associated with complete involution (relative risk 8, 95% confidence interval 0.98–68; P = 0.05).

CONCLUSION
These results suggest that only a renal length of <62 mm on initial US was predictive of complete involution of the MCDK during the follow-up.

KEYWORDS
multicystic kidney, prenatal diagnosis, management, ultrasonography
The effect of time from diagnosis and MCDK length at diagnosis (≥62 mm, green line; <62 mm, red line) on involution, as detected on US. The crosses represent censored values.

FIG. 1.

The effect of time from diagnosis and MCDK length at diagnosis (≥62 mm, green line; <62 mm, red line) on involution, as detected on US. The crosses represent censored values.

PREDICTING THE INVOLUTION OF PRENATALLY DETECTED MCDK

The predictive indices used were based on patient data at the time of entry into the study. The following variables were included in the analysis: gender, affected side (left or right), flank palpation (MCDK palpable or impalpable on first physical examination), MCDK length at first US, and contralateral kidney length and volume on first US. Continuous variables (renal length) were dichotomised using the formula of Han and Babcock [15].

The statistical analysis was conducted in two steps. In the first, a univariate analysis was used to identify variables that were significantly associated with the involution of the MCDK, using the Kaplan–Meier method [16], with differences between patient subgroups assessed by the two-sided log-rank test. A Cox regression model was then applied to identify variables that were independently associated with the involution of the MCDK [17]. Only those variables that were associated with an adverse outcome by univariate analysis (P < 0.25) were included in the Cox regression model [18]; using a backward elimination strategy, those variables that retained a significant independent association with adverse outcome (P < 0.05) were included in the final model. Two end-points were considered for these analyses: (i) the time when MCDK decreased to half the size of the maximum longitudinal length at diagnosis; and (ii) the time when the MCKD became undetectable on US.

Nine of 43 MCDK became undetectable on US, of which five disappeared after 24 (9–122) months of follow-up. The estimated mean (95% CI) time to complete involution of the MCDK was 121 (99–142) months. The Kaplan–Meier estimate of complete MCDK involution showed that 20% were undetectable on US at ≥36 months and half at ≥10 years of age.

The univariate analysis showed that no variables were significantly associated with partial MCDK involution (Table 1). According to our methods, three variables were suitable for inclusion in the multivariate analysis, i.e. gender, palpable kidney and MCDK length (75th percentile). After adjusting by the Cox model, no variable was associated with a decrease in the MCDK to half the size of the maximum longitudinal length at diagnosis.

According to our criteria, four variables were suitable for inclusion in the multivariate analysis, i.e. gender, palpable kidney and MCDK length (at two thresholds, 62 and 72 mm). As an example, the mean time estimated for involution of MCDK of <62 mm long was 100 months (95% CI 70–130). Conversely, the estimated probability for an MCDK of ≥62 mm on initial US was 123 months (95% CI 10–243). The effect of

adverse outcome by univariate analysis variables that were associated with an
We report here an homogeneous series of asymptomatic infants with prenatally detected MCDK. The management was conservative and serial US showed total involution in 20% and partial involution in 67% of the MCDK. The strength of the present study is based on characteristics of its design. All children underwent a systematic protocol and were prospectively followed long-term by the same medical team. In addition, the patients had serial US by the same examiner, with 279 scans in all for analysis. However, we recognize that the relatively few patients limits our conclusion about the predictive factors of MCDK involution.

In this series, there were no cases of malignant transformation over a median follow-up of 50 months. Only two children developed asymptomatic hypertension (one was associated with obesity and the other had spontaneous normalization of blood pressure levels at 12 months) [13,19]. This low rate of complications agrees with most series reported [1,20]. In a computer survey of published work, covering a period of 20 years, Gordon et al. [7] found only six reports of malignancy associated with the MCDK. In a more recent review, we found three other well-documented cases of Wilms’ tumour in children with MCDK [8,9].

In the present study we estimated the rate of partial or complete involution of the MCDK by the Kaplan–Meier method; the mean (95% CI) time for each endpoint was 76 (62–92) and 121 (99–142) months, respectively. On the basis of survival analyses, we estimated that after 3 years of follow-up, 20% of MCDK would become undetectable on US and after 10 years half would show complete involution. Several studies have examined the development of MCDK by US [1,4,5,21–27]; notably, the time for involution estimated by the present Kaplan–Meier analysis is comparable to those reported in multicentre registries with a prolonged follow-up. The preliminary report of the North American MCDK registry showed data from 49 centres in USA and Canada. Of 260 patients enrolled at the registry, 29 were followed for >5 years and seven (24%) MCDK became undetectable by US [1]. Interestingly, the report of a collaborative project from the UK showed similar findings [26]; in that registry, 11 of 46 (24%) MCDK showed complete involution at 2 years of follow-up, three of 21 (14%) at 5 years and two of five at 10 years.

To our knowledge, the present is the first study to evaluate predictive factors associated with the involution of MCDK. In this context, identifying the variables associated with the rate of involution may contribute to establishing a more rational, efficient and cost-effective management of MCDK. Univariate analysis showed that only two variables were significantly associated with complete involution, i.e. a palpable kidney and MCDK length (Table 1). After adjustment by multivariate analysis, only renal length at the initial US (at a threshold of 62 mm) remained associated with complete involution of MCDK. An impalpable kidney was strongly associated with the disappearance of the MCDK on univariate analysis, but this variable did not remain significantly associated with complete involution in the multivariate analysis. This was probably because a palpable kidney and a longer MCDK are normally highly correlated, and this may account for the insignificant finding on multivariate analysis. We found only one study that related renal size and the rate of involution of the MCDK; Rottenberg et al. [5] evaluated 55 children over 32 months and showed that only four of 15 MCDK of ≥60 mm became undetectable on US. Moreover, they found that the involution rate was inversely correlated with the age of the children. The involution rate was −0.5 mm/week for those examined in the first 3 months of life; −0.2 mm/week at 3–12 months and −0.02 mm/week after the first year.

Taken together, these data show a clear tendency of spontaneous involution of MCDK on US, but the slow rate of involution can cause concern about the increased risk of complications associated with MCDK, notably malignant transformation and hypertension. Some authors have advocated surgical removal based on cost-effectiveness and on the advances in surgical technique [28–30]. Nevertheless, we think that thus far there is no strong evidence for the best management of MCDK. Only long-term prospective studies from the neonatal period to adult life can define the natural history of MCDK.

In conclusion, we report the natural history of prenatally detected and clinically managed MCDK. The disappearance rate was slower

### TABLE 1 Predictive factors of the partial and complete involution of MCDK (univariate analysis)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Partial (+)</th>
<th>Partial (–)</th>
<th>log-rank</th>
<th>P</th>
<th>Complete (+)</th>
<th>Complete (–)</th>
<th>log-rank</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>22</td>
<td>23</td>
<td></td>
<td></td>
<td>9</td>
<td>36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender, male/female</td>
<td>13/9</td>
<td>10/13</td>
<td>2.76</td>
<td>0.09</td>
<td>6/3</td>
<td>17/19</td>
<td>0.06</td>
<td>0.80</td>
</tr>
<tr>
<td>Side, right/left</td>
<td>8/14</td>
<td>13/10</td>
<td>0.12</td>
<td>0.73</td>
<td>3/6</td>
<td>18/18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCDK: palpable, present/absent</td>
<td>14/8</td>
<td>10/13</td>
<td>2.46</td>
<td>0.11</td>
<td>8/1</td>
<td>16/20</td>
<td>6.41</td>
<td>0.01</td>
</tr>
<tr>
<td>mean length, &gt;62/≤62 mm</td>
<td>13/9</td>
<td>11/12</td>
<td>0.44</td>
<td>0.50</td>
<td>8/1</td>
<td>18/20</td>
<td>5.28</td>
<td>0.02</td>
</tr>
<tr>
<td>&gt;78/≤78 mm</td>
<td>4/18</td>
<td>8/15</td>
<td>1.48</td>
<td>0.22</td>
<td>9/0</td>
<td>24/12</td>
<td>3.90</td>
<td>0.05</td>
</tr>
<tr>
<td>Contralateral kidney (mean)</td>
<td>7/15</td>
<td>10/13</td>
<td>0.90</td>
<td>0.34</td>
<td>7/2</td>
<td>21/15</td>
<td>1.16</td>
<td>0.28</td>
</tr>
<tr>
<td>&gt;55/≤55 mm</td>
<td>5/17</td>
<td>4/19</td>
<td>0.02</td>
<td>0.89</td>
<td>8/1</td>
<td>28/8</td>
<td>0.02</td>
<td>0.89</td>
</tr>
<tr>
<td>&gt;60/≤60 mm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MCDK length at diagnosis on involution on US is shown in Fig. 1b; there was a significant difference between the survival curves (log-rank 5.28, P = 0.02). On the multivariate analysis, only MCDK length remained marginally significant after backward adjustment by the regression model (hazard ratio 8, 95% CI 0.98–68; P = 0.05).

### DISCUSSION

We report here an homogeneous series of asymptomatic infants with prenatally detected MCDK. The management was conservative and serial US showed total involution in 20% and partial involution in 67% of the MCDK. The strength of the present study is based on characteristics of its design. All children underwent a systematic protocol and were prospectively followed long-term by the same medical team. In addition, the patients had serial US by the same examiner, with 279 scans in all for analysis. However, we recognize that the relatively few patients limits our conclusion about the predictive factors of MCDK involution.

In this series, there were no cases of malignant transformation over a median follow-up of 50 months. Only two children developed asymptomatic hypertension (one was associated with obesity and the other had spontaneous normalization of blood pressure levels at 12 months) [13,19]. This low rate of complications agrees with most series reported [1,20]. In a computer survey of published work, covering a period of 20 years, Gordon et al. [7] found only six reports of malignancy associated with the MCDK. In a more recent review, we found three other well-documented cases of Wilms’ tumour in children with MCDK [8,9].

In the present study we estimated the rate of partial or complete involution of the MCDK by the Kaplan–Meier method; the mean (95% CI) time for each endpoint was 76 (62–92) and 121 (99–142) months, respectively. On the basis of survival analyses, we estimated that after 3 years of follow-up, 20% of MCDK would become undetectable on US and after 10 years half would show complete involution. Several studies have examined the development of MCDK by US [1,4,5,21–27]; notably, the time for involution estimated by the present Kaplan–Meier analysis is comparable to those reported in multicentre registries with a prolonged follow-up. The preliminary report of the North American MCDK registry showed data from 49 centres in USA and Canada. Of 260 patients enrolled at the registry, 29 were followed for >5 years and seven (24%) MCDK became undetectable by US [1]. Interestingly, the report of a collaborative project from the UK showed similar findings [26]; in that registry, 11 of 46 (24%) MCDK showed complete involution at 2 years of follow-up, three of 21 (14%) at 5 years and two of five at 10 years.

To our knowledge, the present is the first study to evaluate predictive factors associated with the involution of MCDK. In this context, identifying the variables associated with the rate of involution may contribute to establishing a more rational, efficient and cost-effective management of MCDK. Univariate analysis showed that only two variables were significantly associated with complete involution, i.e. a palpable kidney and MCDK length (Table 1). After adjustment by multivariate analysis, only renal length at the initial US (at a threshold of 62 mm) remained associated with complete involution of MCDK. An impalpable kidney was strongly associated with the disappearance of the MCDK on univariate analysis, but this variable did not remain significantly associated with complete involution in the multivariate analysis. This was probably because a palpable kidney and a longer MCDK are normally highly correlated, and this may account for the insignificant finding on multivariate analysis. We found only one study that related renal size and the rate of involution of the MCDK; Rottenberg et al. [5] evaluated 55 children over 32 months and showed that only four of 15 MCDK of ≥60 mm became undetectable on US. Moreover, they found that the involution rate was inversely correlated with the age of the children. The involution rate was −0.5 mm/week for those examined in the first 3 months of life, −0.2 mm/week at 3–12 months and −0.02 mm/week after the first year.

Taken together, these data show a clear tendency of spontaneous involution of MCDK on US, but the slow rate of involution can cause concern about the increased risk of complications associated with MCDK, notably malignant transformation and hypertension. Some authors have advocated surgical removal based on cost-effectiveness and on the advances in surgical technique [28–30]. Nevertheless, we think that thus far there is no strong evidence for the best management of MCDK. Only long-term prospective studies from the neonatal period to adult life can define the natural history of MCDK.

In conclusion, we report the natural history of prenatally detected and clinically managed MCDK. The disappearance rate was slower
than those reported in previous studies, according to the survival analysis used here. Only a renal length of <62 mm on initial US was associated with a faster involution of the MCDK during the follow-up.

ACKNOWLEDGEMENTS

This study was partially supported by Fundação de Amparo à Pesquisa do Estado de Minas Gerais (FAPEMIG), Conselho de Desenvolvimento Científico e Tecnológico (CNPq) and Pró-Reitoria de Pesquisa-UFMG.

CONFLICT OF INTEREST

None declared.

REFERENCES

The promise of gene-expression analysis in bladder cancer: a clinician's guide

STEVEN C. SMITH, GARY OXFORD and DAN THEODORESCU
Departments of Urology and Molecular Physiology, The University of Virginia, Charlottesville, VA, USA
Accepted for publication 20 December 2004

INTRODUCTION

Several years since the advent of genomics, the promise of investment in the human genome project has begun to be repaid in full across many areas of science. The most immediate result is the availability of extensive public databases of sequences (e.g. NCBI, Ensembl and ExPASy), from proteins to entire genomes. These resources, coupled with modern advances in robotics and miniaturization, have resulted in the development of many new 'high throughput' technologies based roughly on two differing concepts: either assaying one sample for many different constituent molecules or assaying many samples for one molecule of interest.

Gene-expression analysis of bladder cancer using DNA microarrays represents the former concept, where a single sample of cell line or tissue (Fig. 1) is assayed for the level of expression of a significant number of RNA transcripts, in parallel and under the same experimental conditions [1,2]. Expression of specific genes of interest can be subsequently validated by means of the latter experimental concept: assaying protein expression in parallel across many tissue samples on a human tissue microarray (TMA) via immunohistochemistry (IHC) [3]. The preponderance of published evidence shows that the biological dysregulation that characterises cancer is complex and diverse. As such, high-throughput technologies like microarrays seem an appropriate experimental platform to begin to dissect the pathways that contribute to the development and progression of bladder cancer.

While experimental designs using microarrays devised to identify molecular targets in bladder cancer have been reviewed recently [4,5], as well as array-based advances in the classification of bladder cancer and other neoplasms [6], we seek to both provide an accessible explanation of the technology and review developments from array studies that start to address important clinical questions in bladder cancer. Two such pressing questions are how bladder cancer progresses, and what markers for prognosis can be gleaned from the study of how progression occurs.

A PRIMER ON MICROARRAY TECHNOLOGY

A DNA microarray is a highly miniaturized grid of hundreds to tens of thousands of nucleic acid probes, representative of many known biological sequences, affixed to a solid framework. Because nucleic acids have the property of hybridizing to their complementary sequences, such a framework may be used to assay for the presence of particular sequences in the complex mix of endogenous RNA species that may be isolated from biological samples like bladder cancer tissue or cell lines. The assay begins with isolation and stabilization of total RNA or mRNA from the sample. This sample can be derived from bulk normal or tumour tissue, or microdissected tumour or normal tissue (Fig. 1). Microdissection has allowed a more discrete evaluation of tumour gene expression profiles by effectively excluding most stromal tissues [7]. This step is followed by generation of labelled nucleic acids from this RNA, and hybridization of the mixture to the microarray of probes. Finally, a detector, usually a type of scanner, images the pattern of hybridization and signal intensity of the labelled RNA at probe positions on the grid. Roughly speaking, the presence of a hybridization signal identifies the expression of a particular gene, while the signal intensity is proportional to the level of expression. Two popular platforms of DNA microarrays (Fig. 1) are oligonucleotide microarrays, where short DNA probes of \( \approx 20 \) bp are synthesized directly on a glass chip [8] and cDNA microarrays, where cDNA probes complementary to known genes are spotted on specially prepared microscope slides [9]. In either platform, probes for the expression level of hundreds to tens of thousands of genes of interest are all represented in a grid of barely more than a square centimetre. Oligonucleotide arrays, like those manufactured by the company Affymetrix (www.affymetrix.com), represent a popular standardized approach. These microarrays are grids of thousands of 20–25 bp oligonucleotides selected from known sequences based on design algorithms formulated to choose probes that hybridize to their complements with high affinity and specificity [2,8]. Each fluorescently labelled sample of mixed nucleic acids is hybridized to the array individually, and results represent measures of absolute gene expression levels (Fig. 2A). cDNA microarrays, by contrast, function through simultaneous cohybridization of fluorescently labelled nucleic acids isolated from a test sample, e.g. bladder cancer tissue, and differently labelled nucleic acids from a reference sample, e.g. normal bladder tissue [1,9]. The results therefore represent a ratio of gene expression from the test sample to the reference sample (Fig. 2B). cDNA arrays are commercially available or may be fabricated specifically to assay the experimental system in question [10].

The analysis of microarray data was reviewed recently [11]; the essence of analysing array data is the comparison of gene expression between hybridizations, i.e. the ratio of expression of a gene in one sample to the same gene in another. This concept holds true despite differences in DNA microarray platform, as the comparison can be made of either fluorescence signals of each of the two differentially labelled samples at a probe in one cohybridization cDNA assay, or between fluorescence at a probe on one oligonucleotide array run with each sample [12]. Often, the ratio of expression between experimental and reference samples of sequences probed on the arrays are 'log transformed', to log, values, to give an easier scale to use in further analysis. For example, a ratio of experiment to reference sample gene
expression of 4 : 1, indicating relative up-regulation, would be transformed to \( \log_2 4 = 2 \), and a ratio of 1 : 4, indicating relative down-regulation, would be transformed to \( \log_2 (1/4) = -2 \).

Array data also must be "normalized", so that data may be compared between oligonucleotide arrays or between differentially labelled nucleic acid samples hybridized to the same cDNA array. This process often involves adjusting or scaling all the expression values so that the total signal from each array or from each different fluorescent nucleic acid sample cohybridized is the same, accounting for differences in the amount of starting RNA, or numerous other factors [12].

Microarray studies use a variety of algorithms to manipulate extensive expression data into meaningful patterns [12,13]. Two types of approaches to analysis are unsupervised and supervised. Unsupervised approaches are designed to identify similarity between samples based on expression data, with no a priori grouping of the samples. Commonly, studies use hierarchical clustering algorithms to group samples based on similarity of their gene expression [14]. Alternatively, genes can be clustered based on similarity of their expression across different classes of samples, such as superficial or invasive cancer. Either way, similarity is graphically displayed by proximity on a cluster tree, or dendrogram (Fig. 3). Cluster-analysis images often show clusters of samples and genes in two dimensions, with a graphical representation of relative up-regulation as red and relative down-regulation as green (Fig. 4) [15].

On the other hand, supervised analysis is designed to identify different expression patterns that correlate with a known characteristic of the samples, e.g. histological grade, prognosis, recurrence, etc. Often bladder cancer studies use supervised analyses to determine an optimal "gene
FIG. 2. Differing approaches. (A) Oligonucleotide microarrays. Labelled nucleic acids derived from RNA isolated from two tissue samples are hybridized to arrays individually. Expression results for genes are compared between the assays. (B) cDNA microarrays. Nucleic acids derived from RNA isolated from two tissue samples are labelled with different dyes and then co-hybridized to the same cDNA microarray. Gene expression results are then compared between the samples on the same array.

FIG. 3. Hierarchical clustering. In this representative cluster tree, or dendrogram, similarity is illustrated by proximity on branches of the cluster. In this case, superficial UC samples are shown to cluster together on the left main branch and separately from invasive UC samples on the right main branch. The higher-grade superficial UC sample clusters separately from the two lower-grade superficial UC samples, but it is still on the same main superficial UC branch.
expression signature for tumour classification. These expression signatures may be evaluated either by using an independent test set of tumour samples, or by cross-validation, where each sample is in turn excluded, the remaining samples used to generate an expression signature classifier, and the classifier used to group the excluded sample [15]. An error rate can then be calculated for the classifier, using only the samples tested, when an independent test set of tumour data is unavailable.

Finally, various techniques are used to validate gene expression data garnered from microarrays. Traditional molecular biological techniques such as real-time RT-PCR can verify gene expression at the level of mRNA, immunoblotting can verify translation of mRNA into protein, and IHC can show the pattern of expression on histological sections of tissue. However, one technology that has been useful for validating array data and studies with markers of clinical interest is the TMA [3,16]. Hundreds of cylindrical, 1 mm tissue cores from paraffin-embedded tissue blocks are inserted in a grid into a new paraffin block [Fig. 5] [4,18]. These TMA blocks can then be sectioned and manipulated just as any tissue section. Using this technology, parallel studies of DNA by fluorescence in situ hybridization (FISH), RNA in situ hybridization, or most commonly, protein IHC, may be undertaken on hundreds of tissue samples on a single glass slide. Often, the tissue samples chosen to produce the array have significant known clinical follow-up for correlating the candidate gene expression pattern to the patient's course, therapy response, and outcome.

**USING MICROARRAY TECHNOLOGY TO UNDERSTAND BLADDER CANCER PROGRESSION**

**HUMAN TISSUE STUDIES**

One of the most compelling potential uses of gene expression analysis via microarray technology is to identify molecular markers that correlate with clinical outcome. In one early study, Sanchez-Carbayo et al. [18] used cDNA microarrays to study bladder cancer cell lines to identify differentially expressed genes between distinct histopathological tumour types and stages of disease. Then, they used TMA to validate the potential clinical significance of markers identified in the array studies. Expression of the genes keratin 10 and caveolin-1 was associated with both the presence of squamous differentiation, stage and tumour grade. Further, the expression levels of zyxin, E-cadherin, and moesin were significantly associated with urothelial carcinoma (UC) stage and grade. Membrane moesin expression was significantly associated with overall survival in a subset of 69 patients where the clinical follow-up was available.

More recently, using a larger cDNA microarray platform, the same group analysed gene expression in early-stage and advanced bladder tumours, again with TMA validation for potential markers [19]. Using hierarchical clustering, early-stage tumours clustered together and separately from invasive UC. Gene expression profiling separated carcinoma in situ (CIS) from superficial papillary lesions, and two subgroups with different clinical outcomes within early-stage and invasive tumour clusters were identified. Moreover, expression analysis identified a subgroup of early-stage tumours that gave expression profiles similar to organ-confined invasive lesions, hinting that expression profiling may eventually provide predictive information for patients with early-stage bladder cancer. In analyses targeted to identify genes differentially expressed between early-stage and invasive bladder cancer, the genes, cytokeratin-20, neuropilin-2, p21 and p33ING1, were analysed using TMA. While expression of all these genes was

![Cluster analysis](image-url)

**FIG. 4.** Cluster analysis. In this representative cluster analysis, horizontally across the top, two main types of tissue samples, e.g. superficial UC and invasive UC, shown blue or yellow, are clustered based on similarity of gene expression [15]. Vertically, genes are clustered by similarity of expression pattern across all the samples. By convention, red indicates relative up-regulation and green relative down-regulation.
significantly correlated with tumour stage and grade, only p33ING1 was associated with overall survival. Patients with higher levels of p33ING1 expression had a shorter survival than those with lower expression. The same group also recently reported the use of array technology to identify the tumour suppressor gene, KiSS-1 [20].

Dyrskjot et al. [21] used oligonucleotide microarray analysis of 40 bladder tumours to identify distinct, clinically relevant subclasses of bladder carcinoma. Hierarchical cluster analysis separated the tumours into clusters representing three major stages, Ta, T1 and T2–4, with few outliers. Because of the potential clinical utility of a means to objectively classify tumour samples, they first developed a classifier model using 32 genes to obtain a correlation with pathological staging. This classifier was applied to an independent test set of 68 samples that had been analysed separately using different oligonucleotide array technology, and resulted in a correct classification of 84% of stage Ta, 60% of stage T1 and 74% of stage T2+ tumours. Moreover, the Ta tumours that were misclassified as stage T1 or T2 had a significantly higher likelihood of progression or solid-tumour growth. Additionally, for the Ta samples, an outcome predictor was formulated and tested to ascertain if array data alone could predict the likelihood of recurrence. In cross-validation studies, the outcome predictor correctly classified 75% of the samples as recurrent or not recurrent. The group is currently conducting a 3-year prospective study to explore the potential clinical application for their classifiers.

Most recently, the group used oligonucleotide microarrays to compare superficial UCs with surrounding CIS, UCs with no surrounding CIS, and muscle-invasive UCs [22]. When comparing only a total of 28 superficial UCs with CIS (13 samples) and with no CIS (15 samples), hierarchical cluster analysis separated tumours by presence or absence of CIS, with only one exception. To examine the expression profiles of these two groups, they selected the 50 most up-regulated genes in each group, either UCs with or with no surrounding CIS. The expression profile characterizing the CIS group was present in nearly all of the muscle-invasive UC samples, and was absent in all of the normal bladder biopsies. Surprisingly, the CIS expression profile was even shown by histologically normal biopsies taken from areas adjacent to CIS. Because the presence of CIS is a useful prognostic marker in bladder cancer, a gene expression signature in UCs or in bladder biopsies that identified the presence of CIS.

**FIG. 5.** Construction and use of a TMA. (A) Cylindrical, 1 mm tissue cores are taken from representative areas of paraffin-embedded tissue blocks, guided by pathological examination of previous sections. Tissue cores are then inserted into a grid into a new paraffin block. The resultant TMA block can be sectioned many times for analysis of all the tissue samples in parallel by a variety of techniques [4,18]. (B) Example of TMA application for IHC of RhoGDI2, a gene associated with bladder cancer metastasis [17].
would be clinically useful. To that end, they used cross-validation strategies to generate a 16-gene CIS classifier to identify the CIS gene expression profile, which might be of future use for patients with bladder cancer.

EXPERIMENTAL PROGRESSION MODELS

There are several limitations associated with human tissue studies. One of them is the lack of tissues from metastatic deposits, making the study of the genes associated with the metastatic process difficult. Therefore, to address this deficiency, investigators have derived animal models of bladder cancer metastasis and used these to study the process. For example, several recent publications have shed light on the utility of microarray studies in expanding understanding of the biological mechanisms of bladder cancer progression. Our group recently published the identification of RhoGDI2, an invasion and metastasis suppressor gene in human cancer, based on oligonucleotide microarray analysis of the differences between the noninvasive, minimally metastatic UC cell line T24 and its invasive, aggressively metastatic isogenic variant, T24T [23]. Comparing the most differentially expressed genes between the lines showed that one gene, RhoGDI2, was down-regulated in invasive T24T, and the expression of which (also assayed by microarrays) was inversely correlated to stage and grade in 105 human primary carcinomas. Re-expression of the gene in T24T cells suppressed the invasive and metastatic phenotype, but did not affect in vitro growth, colony formation, or in vivo tumorigenicity, the requirements for a metastasis suppressor. More recently, RhoGDI2 was shown to be an independent predictor for developing metastasis and death from bladder cancer after radical cystectomy, further reinforcing its role as a metastasis suppressor (Fig. 6) [24].

Also, we reported an analysis of the expression profile changes in T24 and T24T using a novel 'positional expression profiling' technique that analysed gene expression data from oligonucleotide microarrays based on chromosomal position [17]. Spectral karyotyping and comparative genomic hybridization were used to fully characterize the cytogenetic abnormalities in these cell lines, and then the functional consequences of the chromosomal rearrangements were assayed by comparing gene expression differences between T24 and T24T based on chromosomal position. In some cases, e.g. the X chromosome, there was a good correlation between higher chromosomal dosage and higher expression in T24 than T24T; however, in many cases there is a less direct correlation between chromosomal abundance and gene expression. The group also used microarray technology to analyse a cell-line progression series of increasing metastatic potential, generated through repetitive cycles of passage of T24T through lung metastases and culture of resultant metastases [25]. These results, when combined with microarray analysis of human bladder cancer, identified genes associated with bladder cancer lung metastasis that may eventually prove to be targets for future therapy. Clearly, DNA microarray technology will continue to be an important tool for studying models of bladder cancer progression.

DISCUSSION

Often, when considering developments like these, the question becomes a matter of how or when technologies based on or derived from the results of expression analysis might become generally available or relevant in patient care. It is very attractive to consider that, with time and prospective validation, prognostic markers for recurrence might be one day used to provide increased vigilance of follow-up in subsets of patients with CIS, or trigger the use of adjuvant chemotherapy in patients at high risk of metastasis after cystectomy [24]. Unfortunately, such prospective trials have been difficult but were recently facilitated by the establishment of organizations such as the National Cancer Institutes’ Early Detection Research Network in the USA (http://www3.cancer.gov/prevention/cbrg/edrn/index.html).

Most likely, new tests based on technologies that have proven to be of some clinical utility in the past will be the first to be validated prospectively and become available for clinical use. One example of this is the international validation effort for p53 as a prognostic factor for bladder cancer invasion [26]. In this model, gene expression analysis using microarray technology can serve as a ‘high-throughput’ means to discover markers that distinguish between clinically relevant classes of tumour. As growing databases of tumour data become available for analysis, there is great hope that interventions tailored to an individual’s tumour phenotype, based on a panel of initial tests, may become a reality. Such an approach is called ‘pharmacogenomics’, where the drugs used are personalized to the genetic constitution of a particular patient and tumour.

FIG. 6. Association between RhoGDI2 status and disease-free survival time. Comparison of Kaplan-Meier estimates of disease-free survival between patients with RhoGDI2 positive tumours (red) and those with reduced or absent protein expression (green) (P < 0.0001) [24]. Typical IHC results are shown in Fig. 5B.
In the long term the use of gene-expression analysis techniques will lead to an understanding of tumour biology. As teleologically, a cancer cell is the product of the genes it expresses, analysing these through technologies like microarrays will provide the insight required into what molecules and processes contribute to the phenomenon of bladder cancer and progression. In the end, these are the insights that will undoubtedly engender the greatest difference in the diagnostic and therapeutic approach to bladder cancer.

ACKNOWLEDGEMENTS

The authors thank Dr Christopher Moskaluk and Mr Alex Baras for their helpful suggestions.

CONFLICT OF INTEREST

None declared.

REFERENCES

2 Lipshutz RJ, Fodor SP, Gingeras TR, Lockhart DJ. High density synthetic oligonucleotide arrays. Nat Genet 1999; 21 (Suppl. 1): 20–4

Correspondence: Dan Theodorescu, Department of Urology, Box 424, University of Virginia Health Sciences Center, Charlottesville, Virginia, 22908, USA. e-mail: dt9d@virginia.edu

Abbreviations: FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; UC, urothelial carcinoma; CIS, carcinoma in situ; TMA, tissue microarray.
Synergistic inhibitory effect of high-intensity focused ultrasound combined with chemotherapy on Dunning adenocarcinoma

PHILIPPE PAPAREL, LAURA CURIEL*, SABRINA CHESNAIS*, RENE ECOCHARD† JEAN-YVES CHAPELON* and ALBERT GELET

Urology, Edouard Herriot Hospital, *INSERM, and †Biostatistics, Hospices Civils de Lyon, Lyon, France

Accepted for publication 21 November 2004

OBJECTIVE

To evaluate the therapeutic effect of high-intensity focused ultrasound (HIFU) combined with chemotherapy (paclitaxel + estramustine) on AT2 Dunning adenocarcinoma, as no satisfactory treatment for localized prostate cancer is available for patients with a poor prognosis, e.g. stage T3, a high Gleason score, or a prostate-specific antigen level of >15 ng/mL.

MATERIALS AND METHODS

Forty-one Dunning AT2 tumour-bearing Copenhagen rats were divided into four groups, i.e. control, chemotherapy, HIFU, and chemotherapy + HIFU (the last three treated for 1 week). The growth in tumour volume was recorded for 3 weeks, the point at which tumour volume was considered to have doubled (doubling time). The growth curves of each group were plotted and evaluated statistically.

RESULTS

At 30 days of follow-up the distributions of tumour volume with treatment group were significantly different (P < 0.001); volumes were significantly greater in the control than in the chemotherapy-only or in the HIFU-only group (both P = 0.006). The greatest difference was between the chemotherapy + HIFU and the control group. The tumour doubling times were 13.2 days for HIFU-only, 31.2 days for chemotherapy + HIFU and 7.7 days for the controls.

CONCLUSION

These results suggest that this combined therapy could be useful for treating patients with high-risk prostate cancer.

KEYWORDS

prostate cancer, paclitaxel, estramustine phosphate, Dunning model, HIFU
To treat the tumour several pulses were applied following the model shown in Fig. 1, each with an acoustical power of 13 W for 5 s with a 5-s waiting-time between them, and separated by a step of 1.6 mm. Under general anaesthesia, the animal was placed on a specially designed Plexiglas gantry with an opening below the abdominal area for the penetration of ultrasound. The tumour was immobilized with a silicone ring fastened to the gantry. This gantry was then mounted on the three-axis positioning system to roughly position the animal over the firing arm at the approximate focal distance. The tank was then filled with warm (35 °C) degassed and deionized water. The ultrasonographic probe was then used to make an image before the pulses, to define the treatment zone. The coordinates of the target volume were sent to the instrument computer which controlled the movements of the HIFU transducer. Programming by the computer software produces several pulses according to the target volume, the dimension of which corresponds to 75% of the tumour volume. A HIFU-lesion model [16] was used to predict the lesion volume under the actual conditions and then the number of pulses calculated to cover 75% of the tumour volume.

Two chemotherapy agents were used: paclitaxel (Taxane, Bristol-Myers-Squibb, USA) as a subcutaneous injection at 4 mg/kg; and estramustine phosphate (EMP, Estracyt, Pharmacia & Upjohn, SA) by intraperitoneal injection at 15 mg/kg. Fifteen days after implanting the tumour, when the tumour was ≈10 mL, the rats were separated into four groups; controls (six), HIFU-only (11), chemotherapy-only (12) and HIFU + chemotherapy (12). The treatment lasted 5 days and followed the treatment protocol given in Table 1.

The rats were weighed and the tumour volume measured weekly; over the course of tumour growth in the weeks after treatment, the rats were killed if the tumour was >60 mm in diameter or if the tumour volume was such that the rats were no longer able to move. The tumours were photographed in two dimensions each week with a scale allowing a precise measurement; tumour volume was then calculated as length \( \times \) width \( \times \) height \( \times 0.5236 \) [17].

The distributions of tumour volume at 30 days of follow-up were compared overall using a nonparametric ANOVA (Kruskal–Wallis test) and then more specifically, each group was compared with the others (Mann–Whitney U-test) with a Bonferroni correction to keep the overall significance level of the comparison tests at \( P < 0.05 \).

The effects of chemotherapy, HIFU and their interaction on tumour volumes were analysed using linear regression for repeated measurements after a logarithmic transformation of the volumes. The results of this regression analysis were expressed as percentages of volume increase per day and as tumour doubling times in days.

### RESULTS

Some of the animals did not survive the complete follow-up because they died before the threshold dates (Table 1). The distributions of tumour volume according to the treatment group were significantly different (\( P < 0.001 \); Table 1). The volumes were significantly greater in the control group than in the chemotherapy-only group (\( P = 0.006 \)) or in the HIFU-only group (\( P = 0.006 \)). The greatest difference was between the

<table>
<thead>
<tr>
<th>Protocol or variable</th>
<th>HIFU + chemotherapy</th>
<th>HIFU alone</th>
<th>Chemotherapy alone</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 days EMP</td>
<td>–</td>
<td>–</td>
<td>EMP</td>
<td>–</td>
</tr>
<tr>
<td>16 paclitaxel</td>
<td>–</td>
<td>–</td>
<td>paclitaxel</td>
<td>–</td>
</tr>
<tr>
<td>17 HIFU</td>
<td>HIFU</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>18 paclitaxel</td>
<td>–</td>
<td>–</td>
<td>paclitaxel</td>
<td>–</td>
</tr>
<tr>
<td>19 EMP</td>
<td>–</td>
<td>–</td>
<td>EMP</td>
<td>–</td>
</tr>
</tbody>
</table>

### TABLE 1: Days and administration protocols for HIFU treatments and chemotherapy. Dosage was 15 mg/kg for EMP and 4 mg/kg for paclitaxel, the distribution of tumour volumes at 30 days and the percentage growth/day

<table>
<thead>
<tr>
<th>Protocol or variable</th>
<th>HIFU + chemotherapy</th>
<th>HIFU alone</th>
<th>Chemotherapy alone</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 days EMP</td>
<td>–</td>
<td>–</td>
<td>EMP</td>
<td>–</td>
</tr>
<tr>
<td>16 paclitaxel</td>
<td>–</td>
<td>–</td>
<td>paclitaxel</td>
<td>–</td>
</tr>
<tr>
<td>17 HIFU</td>
<td>HIFU</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>18 paclitaxel</td>
<td>–</td>
<td>–</td>
<td>paclitaxel</td>
<td>–</td>
</tr>
<tr>
<td>19 EMP</td>
<td>–</td>
<td>–</td>
<td>EMP</td>
<td>–</td>
</tr>
</tbody>
</table>

Median (interquartile range) [range]

<table>
<thead>
<tr>
<th>Tumour volume, mL</th>
<th>Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.47 (0.25–13.00)</td>
<td>EMP</td>
</tr>
<tr>
<td>26.40 (20.83–29.04)</td>
<td>paclitaxel</td>
</tr>
<tr>
<td>26.95 (21.25–29.61)</td>
<td>HIFU</td>
</tr>
<tr>
<td>26.95 (21.25–29.61)</td>
<td>paclitaxel</td>
</tr>
<tr>
<td>74.72 (73.50–104.75)</td>
<td>EMP</td>
</tr>
</tbody>
</table>

Mean (95% CI) % increase/day

<table>
<thead>
<tr>
<th>P</th>
<th>Tumour doubling time, days</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;0.05</td>
<td>31.2</td>
</tr>
<tr>
<td>&lt;0.001</td>
<td>10.8</td>
</tr>
<tr>
<td>&lt;0.001</td>
<td>13.2</td>
</tr>
<tr>
<td>&lt;0.001</td>
<td>7.7</td>
</tr>
</tbody>
</table>

### FIG. 1. Pulse position and order during HIFU treatment.

![Diagram](image-url)
The mean tumour volume with time for the four groups (red dotted line, HIFU + chemotherapy; green solid line, chemotherapy only; light red dash/dot, HIFU only; light green dashed, control) from 8 days after HIFU treatment (at 24 days).

**FIG. 2.**

The mechanism of tissue destruction by HIFU is complex. Ultrasound energy applied to tissues results in mechanical stress of the cells, causing changes in the biological system. Three effects can be distinguished during ultrasound exposure, i.e. mechanical, thermal and cavitation-induced; the presence of each depends on the field intensity and they are frequently interdependent [18].

The mechanical interaction includes radiation force, radiation torque and streaming, and causes direct changes in the biological system. The thermal effect is associated with the absorption of ultrasound energy in the tissue, which is then converted into heat. The biological changes induced by this heating are determined by the temperature reached and the duration of the exposure. The lesion extension is determined where a dose threshold is reached. For thermal doses above the threshold, irreversible damage is induced in the tissue as coagulation necrosis. For thermal doses below the threshold, the effect depends on the tissue sensitivity to heat [19].

At high intensities the biological effects associated with the activity of cavitation bubbles appear. Much living tissue contains sites at which microbubbles will form in response to pressure variations. Bubbles of a certain diameter will resonate depending on the frequency of the wave. Indeed, even bubbles that are not large enough to resonate increase their diameter by a phenomenon termed 'rectified diffusion' and the cavitation is enhanced. At higher intensities the bubble increases in size and suddenly collapses, producing shock waves with enormous pressure, up to 2–3 GPa, thus causing mechanical stress and temperatures that can reach several thousand degrees Kelvin. This results in the formation of free radicals which are chemically active. However, despite the force of this reaction, the phenomenon remains localized at the level of the cavitation bubble and spreads for only a few micrometres [20].

In addition to the mechanical, thermal and cavitation effects, another can be present when during HIFU; because of heat accumulation from thermal effects, the temperature increase can cause boiling. Bubbles of steam can then form at the focus and act as a mirror for the ultrasound, preventing the energy from reaching the tissue underneath this boiling region [18].

In clinical practice, the efficacy of HIFU for localized cancers is high, but all authors report the appearance of residual cancerous tissue in 6–17% of treated patients [21–23]. The persistence of malignant cells within prostatic tumours treated by HIFU is probably explained by the presence in the target zone of macrobubbles of several millimetres in diameter, provoked by the intracellular boiling of the water. These macrobubbles form a screen for the HIFU beam. Zones insufficiently treated persist beneath the boiling zones; this phenomenon could be amplified when tissues are highly vascularized, in particular within tumours that are very undifferentiated. For large tumours (clinical stage T2b–T3), the persistence of malignant cells is explained by the frequent capsular extension (the tumour invades the periprostatic fat). As HIFU is limited to the gland, cells situated in the periprostatic fat (outside the capsule) are not in the field of the ultrasound beam.

The objective of the present study was to reproduce the clinical situation, to assess whether some malignant cells escape destruction by HIFU, either within the tumour or at its periphery. Hence we used a partial treatment limited to 75% of the tumour volume; the results show that the response was supra-additive when chemotherapy and HIFU were administered simultaneously.

Others have reported animal models in which HIFU associated with chemotherapy gave better results than treatment with HIFU alone. Fry and Johnson [14] reported an additive effect of HIFU + carmustine on the medulloblastome of the hamster; the rate of healing after HIFU only was 29%, vs 40% with HIFU + carmustine. Yang et al. [13] reported better survival in a hepatoma model (Moris 3924 A implanted in the rat) when combining HIFU and doxorubicin or HIFU and Adriamycin. However, in these studies, the difference between the chemotherapy and HIFU group and the HIFU-only group was not significant. Moore et al. [11] reported a similar result in the same animal model (hepatoma 3924 A) by using cyclophosphamide. The interaction mechanism of HIFU and chemotherapy is not yet known. Yang et al. [12] suggested it could be related to a better intracellular diffusion of the chemotherapy agent after concomitant HIFU + chemotherapy and the control group, but that difference was not significant because there were too few rats.

In all 41 rats at 15 days of follow-up the mean (SD) tumour volume was 9.4 (3.3) mL; this volume increased rapidly in the controls, HIFU-only and the chemotherapy-only groups, but in the HIFU + chemotherapy group the mean increase in tumour volume was 2.2%/day (and not significantly different from zero; Table 1 and Fig. 2). The increase in tumour volume can also be expressed as the tumour doubling time, also shown in Table 1.

The objective of the present study was to reproduce the clinical situation, to assess whether some malignant cells escape destruction by HIFU, either within the tumour or at its periphery. Hence we used a partial treatment limited to 75% of the tumour volume; the results show that the response was supra-additive when chemotherapy and HIFU were administered simultaneously.

Others have reported animal models in which HIFU associated with chemotherapy gave better results than treatment with HIFU alone. Fry and Johnson [14] reported an additive effect of HIFU + carmustine on the medulloblastome of the hamster; the rate of healing after HIFU only was 29%, vs 40% with HIFU + carmustine. Yang et al. [13] reported better survival in a hepatoma model (Moris 3924 A implanted in the rat) when combining HIFU and doxorubicin or HIFU and Adriamycin. However, in these studies, the difference between the chemotherapy and HIFU group and the HIFU-only group was not significant. Moore et al. [11] reported a similar result in the same animal model (hepatoma 3924 A) by using cyclophosphamide. The interaction mechanism of HIFU and chemotherapy is not yet known. Yang et al. [12] suggested it could be related to a better intracellular diffusion of the chemotherapy agent after concomitant
increases in permeability of the cell membrane and from high intratumoral blood flow. In the present study assessing partially treated tumours and chemotherapy before and after HIFU, two explanations for the synergistic effect are possible. The first would be that chemotherapy before HIFU degrades the cells by a cytotoxic effect and thus favours their destruction during HIFU. The second hypothesis is that the cells at the periphery of the tumour and outside the zone treated by HIFU are degraded by the diffusion of the ultrasound beam. This diffusion is increased by the presence of cavitation bubbles within the target zone. The cells affected by this diffused ultrasound beam consequently become more sensitive to the action of chemotherapy. A weak acoustic intensity would be sufficient to produce this effect. Saad and Hahn [24] showed in vitro that exposure to ultrasound with an intensity of 1 W/cm² increased the action of doxorubicin. Yumita and Umemura [25] obtained a similar result on a colon cancer model by using chloroaaluminium phthalocyanine and an acoustic intensity of 3 W/cm². Finally, Yu et al. [26] also showed a synergistic effect on an ovarian cancer model by using adriamycin and an acoustic intensity of 7.84 W/cm².

In clinical practice, the association of HIFU and chemotherapy could be used for patients with prostate cancer who are at high risk of recurrence, either because of an aggressive tumour (undifferentiated Gleason 4 + 3 and higher) or regional extension of the tumour (stage T2b–T3). Indeed, the efficacy of the taxane-EMP combination was reported in humans; Oudart et al. [27] showed in a randomized study that combined docetaxel and EMP was more effective than mitoxantrone or prednisolone combined. The biological response was a reduction in the PSA level of more than half, 67% and 18%, respectively (P < 0.001) and an overall survival rate 18.6 vs 11.6 months (P = 0.08). The feasibility of neoadjuvant chemotherapy by taxane has already been tested before radical prostatectomy in high-risk patients [28].

In conclusion, the present results indicate that combined treatment using chemotherapy and HIFU has a synergistic effect on prostate cancer progression through a prolonged slowing of tumour growth, suggesting that such combined therapy could be useful for treating high-risk prostate cancer.

CONFLICT OF INTEREST
None declared. Source of funding: INSERM.

REFERENCES
22. Gelet A, Chapelon JY, Bouvier R, Pangaud C, Lasne Y. Local control of


Correspondence: Philippe Paparel, Department of Urology, Edouard Herriot Hospital, Lyon, France.
e-mail: paparephilippe@aol.com

Abbreviations: HIFU, high-intensity focused ultrasound; EMP, estramustine phosphate
Stereotactic electrical stimulation of the pontine micturition centre in the pig

ASGER L. DALMOSE, CARSTEN R. BJARKAM* and JENS CHRISTIAN DJURHUUS†
Department of Urology, Hospital of Aalborg, Aalborg, *Institute of Anatomy and †Institute of Experimental Clinical Research, University of Aarhus, Århus, Denmark
Accepted for publication 21 November 2004

OBJECTIVE
To apply stereotactic electrical stimulation of the pig brainstem and thus identify a pontine micturition centre.

MATERIALS AND METHODS
In 10 anaesthetized female Vietnamese minipigs a needle-electrode was positioned in the pontine region. Pressure responses in the lower urinary tract identified the micturition centre functionally during electrical stimulation. Stereotactic coordinates were recorded, and the needle visualized by fluoroscopy, magnetic resonance imaging (MRI) or histologically.

RESULTS
The stimulation evoked responses similar to voiding, i.e. a urethral pressure decrease followed by a bladder pressure increase; or similar to a continence manoeuvre, i.e. urethral pressure increase and no change in bladder pressure. In a few cases a continence response was evoked by stimulating a site 1 mm away from the site where a voiding response was evoked. The electrode position was detected by the fluoroscopy-based stereotactic procedure followed by subsequent MRI (one animal), and by histological analysis, verifying it to be in the dorsolateral pontine region.

CONCLUSIONS
These results show that a pontine micturition centre exists in pigs similar to that described in rats, cats, dogs and humans.

KEYWORDS
central nervous system, pons, micturition, Sus scrofa, stereotactic technique

INTRODUCTION
One of the early stereotactic studies on micturition was in cats, showing a pontine micturition centre (PMC) crucial for the control of urine storage and voiding [1]. A PMC has also been detected by stereotactic procedures in rats and dogs, and in humans by positron-emission tomography and in clinical cases of brainstem disease [2–5].

Pigs have been used increasingly in research on the regulation of voiding function because of their anatomical and physiological resemblance to humans [6–9]. The aim of the present study was to identify and locate a PMC by transurethral recording of lower urinary tract pressures during stereotactic electrical stimulation of the pontine region.

MATERIALS AND METHODS
Ten female Vietnamese minipigs (Sus scrofa, 30–70 kg) were used in accordance with a protocol approved by the Danish Board on Research Animals. The animals were sedated with ketaminol 10 mg/kg, midazolam 0.5 mg/kg and etomidatum 0.5 mg/kg, and then intubated and kept on assisted ventilation with 1–3.5% isoflurane in a 33% O
2 and 67% N
2 mixture, with continuous monitoring of heart rate, blood-oxygen saturation and temperature.

Cadaver studies had established the location of the arteriolar formation 'rete mirabilis' 1–2 cm anterior and 1–2 cm rostral to the anterior surface of the pons. The pigs were placed prone and an arterial catheter (Cordis, Johnson and Johnson, Miami, Florida) was inserted, during repeated infusion with contrast medium (Visipaque, Amersham Health, Princeton, New Jersey) and fluoroscopy guidance (Exospec CB 7–D, Ziehm, Kraus GmbH, Germany), into the internal carotid artery just proximal to the rete mirabilis.

A transurethral separation catheter made of a 16 F silicon double-lumen bladder catheter (Rüsch, Kernen, Germany) was used to record lower urinary tract pressures. It had a 5 F silicone catheter (Vygon, Ecouen, France) attached with a side-opening 1 cm proximal to the balloon of the bladder catheter, for urethral pressure recording [10]. The 10 mL balloon of the separation catheter was retracted to the bladder base to stabilize it and serve as a watertight seal between bladder and urethra. One lumen of the bladder catheter was used for continuous adjustment, to keep the bladder volume at 50–100 mL. The other lumen and the attached catheter was perfused with saline and connected to pressure transducers (Truflow, Baxter, Santa Ana, California). The pressures and the stimulations were recorded on a computer (Dantec Menuet, Medtronic, Skovlunde, Denmark).

The head of the pig was fixed in a stereotactic frame (Stoelting, Wood Dale, Illinois, USA) by bilateral bone-screws inserted into the zygomatic arc directly below the lateral margin of the eye (Fig. 1). The skin was removed from the vertex and the pig’s head position locked with a bar placed over the snout, so that the skull surface 3 cm anterior to the bregma was 7 mm lower than the bregma, thus defining the horizontal plane. A 3 × 5 cm hole was made in the skull giving access to the frontal sinus, which in adult pigs stretches almost to the line where the trapezoid muscle inserts. A 2 × 3 cm hole was made in the floor of the frontal sinus, the underlying dura cut open, and the brain exposed.

A tungsten-needle electrode (WPI, Sarasota, Florida) was inserted through a lumbar puncture cannula (Sensi Touch, Kendahl, Mansfield, Massachusetts) into the pontine region of the first three animals, guided by repeated fluoroscopic visualization of the needle electrode relative to the rete mirabilis, until stereotactic coordinates were established (Fig. 2), enabling positioning of the needle electrode in the remaining seven pigs based on the obtained stereotactic coordinates. The electrode was connected to a custom-made battery-driven unit enabling stimulation with the following parameters: pulse width 100 μs; frequency 30 pulses/s; amplitude 10–40 μA. The stereotactic mapping was then performed in 1-mm steps in all three planes during subsequent transurethral pressure recording, until an electrode position that elicited transurethral bladder responses was identified.

For histological specimens the brain was perfused with 4% formaldehyde injected under high pressure into one common carotid artery. The brain was then removed and dehydrated before paraffin embedding and coronal microtome sectioning into 10 μm thick sections. The sections were Nissl-stained with 0.1% toluidine blue in citrate buffer (pH 4.0) at room temperature for 4 min, followed by a rinse in distilled water, differentiation through 99% alcohol, clearing in xylol and mounting (DePex, Laboratory Supplies, Poole, England).

One of the pigs with a voiding response was assessed by MRI in a 1.5 T scanner (Signa, General Electric, Milwaukee, Wisconsin) with the needle electrode left in place.

RESULTS

The stimulation evoked responses similar to voiding, i.e. a urethral pressure decrease followed by a bladder pressure increase.
or similar to a continence manoeuvre, i.e. a urethral pressure increase and no change in bladder pressure (Fig. 4).

The responses were evoked from oval zones in the pontine region with a longitudinal rostro-caudal axis and measuring 1–3 x 1–7 mm. Voiding responses were elicited from sites with coordinates in the three planes of (relative to the bregma); posterior 0–8 mm, lateral 3–10 mm, and depth 51–69 mm. Continence responses were elicited from sites with coordinates in the three planes of (relative to the bregma); posterior 0–5 mm, lateral 5–10 mm, and depth 43–60 mm. In a few cases a site responsible for, e.g. a voiding response, had a site responsible for a continence response directly next to it, so that a 1-mm change in needle tip location would evoke reciprocal results (Fig. 5).

The range of pressures in the voiding response was a bladder pressure increase of 3–7 cmH₂O and a urethral pressure decrease of 10–35 cmH₂O (Fig. 3). The range of pressure increase of the continence response was up to 45 cmH₂O (Fig. 4). The delay from onset of stimulation to the pressure response was 11–21 s in the voiding responses and 7–13 s in the continence responses.

MRI immediately after the experiment in one of the pigs with a voiding response, and histological analysis in the others, showed that the stimulation sites were in the pons (Fig. 6).

DISCUSSION

Pontine areas capable of evoking either voiding or continence responses in the lower urinary tract were detected reproducibly. In other species related areas have been reported and the term PMC is now established both in human studies and animal research [1,2,4,11].

In pigs, most urodynamic studies so far have focused on the lower urinary tract and only a few anatomical studies of the role of the CNS in regulating voiding and continence have been published [7,12]. The value of having identified a porcine PMC is considerable, as pigs have well-established functional and anatomical similarities with humans [6,8,9]. The large pig brain (6 x 5 x 4 cm) is advantageous as it enables complicated surgical procedures and the use of neural
stimulation devices intended for human use. The size of the pig brain also enables the use of fluoroscopy and MRI equipment for clinical use, which makes in vivo monitoring of stereotactic procedures and the position of implants, and thus chronic studies, possible [7].

In the voiding responses the urethral relaxation preceded the bladder response by <1 s; not only was the urethral response earlier than the bladder response in these pigs, it was also much larger (Fig. 3). The sequential activation of the two structures and the difference in pressure patterns was similar to that of normal female humans [13] and female pigs [14], but it is unclear whether these exact patterns are present in voiding in cats [15], rats [2] and dogs [11]. This is a clinically important aspect, as some lower urinary tract disorders are characterized by premature [16] or isolated [17] urethral relaxation, and therefore the pig seems to be highly relevant as a research animal for investigating diseases of urinary storage function.

In conclusion, the present results show that a PMC exists in pigs, similar to that described in rats, cats, and dogs in humans. This allows very relevant experiments, as the pig is urodynamically similar to humans, and the large pig brain permits good anatomical accuracy.

ACKNOWLEDGEMENTS

This study was supported by The Danish Health Research Council, the University of Aarhus Research Foundation, The Sahva Foundation, and The Mads Clausen Foundation.

CONFLICT OF INTEREST

None declared.

REFERENCES


Correspondence: Asger L. Dalmose, Christian Winthers Vej 10, DK-8230 Åbyhøj, Denmark. e-mail: asger.dalmose@daldnet.dk

Abbreviations: PMC, pontine micturition centre.
Gene transfer of vasoactive intestinal polypeptide into the penis improves erectile response in the diabetic rat

ZHOU-JUN SHEN, HUA WANG, YING-LI LU*, XIE-LAI ZHOU, SHAN-WEN CHEN and ZHAO-DIAN CHEN
Department of Urology, 1st Affiliated Hospital and *Department of Endocrinology, Sir Run Run Shao Hospital, Medical School of Zhejiang University, Hangzhou, PR China
Accepted for publication 8 November 2004

OBJECTIVES
To determine the feasibility of transfecting penile corpora cavernosa with pcDNA3/vasoactive intestinal polypeptide (VIP) cDNA, which encodes for VIP in streptozotocin (STZ)-diabetic rats, to clarify whether transfection ofVIP cDNA into the cavernosum affects the physiological response to cavernosal nerve stimulation, and whether this process would affect other organs in the diabetic rat model in vivo.

MATERIALS AND METHODS
pcDNA3/VIP cDNA was injected into the corpus cavernosum of STZ-induced diabetic Sprague-Dawley rats. The intracavernosal pressure (ICP) and response to electrical stimulation of the cavernosal nerve (15 Hz, 1.5 ms, 20 V, 1 min) were measured in subsamples of rats at 1, 3, 7 and 14 days after injection; after measuring the ICP the animals were killed, and penile, hepatic, renal artery and abdominal aorta tissue samples were frozen in liquid nitrogen and stored at −80°C. The gene expression of VIP in all samples, assessed as the expression of VIP mRNA, was estimated using a semiquantitative reverse-transcription polymerase chain reaction.

RESULTS
The mean amplitude of ICP and expression of VIP mRNA in the cavernosa of the VIP-treated rats was greater at 1, 3, 7 and 14 days after injection (P < 0.05) than in the control animals. There were no changes in the expression of VIP mRNA in hepatic, renal and abdominal aorta samples after injection (P > 0.05).

CONCLUSIONS
VIP cDNA is easily incorporated into corpus cavernosum, and the expression is sustained for ≥2 weeks in the penis in vivo. The transfer of VIP is capable of altering the physiologically relevant erectile response, as measured by an increase in the ICP after stimulating the cavernosal nerve. The intracorporal micro-injection of pcDNA3/VIP cDNA had little effect on the expression of VIP mRNA in other important organs.

KEYWORDS
vasoactive intestinal polypeptide, gene transfer, penis, diabetes mellitus, rat
GENE TRANSFER OF VIP INTO PENILE CORPUS CAVERNOSUM

Diabetes was induced in male Sprague-Dawley rats (200–300 g at onset) by one intraperitoneal injection with streptozotocin (STZ, 65 mg/kg). Controls received the citrate buffer carrier alone. Rats were accepted as diabetic if the whole-blood glucose level was ≥16.0 mmol/L, as measured with a glucometer (Advantage, Roche, USA) in whole blood taken from the proximal ventral tail vein. These rats were maintained in alternating cycles of darkness (18.00 to 06.00 hours) and light (06.00 to 18.00 hours). Food and water were freely available. Finally, 61 rats were accepted as diabetic and used in the study at 10 weeks after treatment.

The 61 diabetic rats were randomly divided into groups A–D of 15 rats each (16 in D), with the ICP measured after injection, then at 3, 7 and 14 days after injection, respectively. Each group was subdivided into subgroup 1 (sham-operated), and an intracorpal injection with 200 μL PBS containing 20% sucrose), 2 (as 1, but with 100 μg pcDNA3 vector) and 3 (as 1, with gene therapy with the pcDNA3/VIP cDNA). Before injection, animals were anaesthetized with pentobarbital sodium (35 mg/kg). A midline incision was made to expose the penis, and blood flow to the penis occluded by securely tying a length of rubber band at the base of the organ. Injections were delivered into the corpus cavernosum with a 1-ml insulin syringe. The ligature was removed after 30 min and the incision closed. Basal and nerve-stimulated ICP was measured at 1, 3, 7 and 14 days after injection, respectively.

Finally, tissues (penile, liver, kidney and abdominal aorta) for VIP mRNA determination were harvested after measuring ICP, immediately frozen in liquid nitrogen and stored at −80°C. The VIP cDNA (≈ 500 nucleotides; i.e. 0.5 kb) was inserted into the pcDNA3 vector, where expression is considered significant at $P < 0.05$. The effects of electrostimulation of the cavernosal nerve on the ICP in vivo was used to evaluate the potential physiological relevance of any change in expression of VIP in the different groups; the results are shown in Table 1. There was a significant difference in the mean ICP between the controls (i.e. sham-operated with PBS or vector only, subgroup 1 and 2) and VIP-treated rats ($P < 0.05$) at all times after treatment.

The expression of VIP mRNA in the corpus cavernosum, liver, kidney and abdominal aorta of all groups is also shown in Table 1. There was a significant difference between the corpus cavernosum of the control and the VIP-treated rats ($P < 0.05$) at 1, 3, 7 and 14 days after treatment, but no significant difference in hepatic, renal and abdominal aorta VIP mRNA among the three subgroups ($P > 0.05$) at any time after treatment.

DISCUSSION

Various mechanisms have been suggested for the erectile disorders associated with diabetes. Vascular disease and neuropathies resulting from diabetes are frequently underlying causes of impotence in younger men. Autonomic neuropathy can account for decreased function of erectogenic nerves or an altered balance of the pro-erectile and anti-erectile transmitters reaching the cavernosal smooth muscle. The vascular supply of the penis is highly sensitive to atherosclerotic changes, which are
accelerated in diabetic men. In the human, psychological factors often add to these organic disturbances.

The pathophysiology of diabetic ED has yet to be completely elucidated, but in vitro work showed that corporal smooth muscle from men with diabetes had less autonomically mediated or endothelium-dependent relaxation than tissues from non-diabetic counterparts [20]. A more recent immunohistochemical study suggested that advanced glycation end products in diabetic men, when deposited within the penile tunica and corporal collagen, might result in down-regulation of NOS through modulation of endothelial NOS and/or inducible NOS enzymatic activity [21]. Although NO is considered the neurotransmitter responsible for mediating the relaxation of the corpora cavernosa, it may be not be the only factor involved, because mice lacking neuronal NOS mate successfully [22]. VIP, which is found at high concentrations in the terminals of the major pelvic ganglia [23] and deep arteries of the penis, and in nonvascular smooth muscle tissue of the corpus cavernosum and corpus spongiosum [24], may also have a role in the ED associated with diabetes. There are fewer VIP-immunoreactive fibres in penile tissue from impotent men with diabetes [25] and from STZ-diabetic rats [26]. VIP-like immunoreactivity was detected in the pudendal vein effluent after pelvic nerve stimulation [27], showing that the VIP-containing secretory vesicles found within cholinergic nerve endings in the penis undergo exocytosis when these endings are invaded by action potentials, as is also found during erection [28,29]. VIP can stimulate sexual behaviour and enhance the penile tumescence, is mediated by a cAMP mechanism, after its activation by adenylate cyclase [7,8].

Therefore, treatment that potentiates the effects of NO/VIP is a rational therapeutic alternative if there is potentially attenuated NO/VIP output. Sildenafil improves erectile function in men with ED [33–35] because it facilitates relaxation of smooth muscle cells that have become dysfunctional during the ageing and/or diabetic process. However, not every man with ED responds to sildenafil, mainly because its effect depends directly on the concomitant release of NO from the cavernosal nerve terminals. However, this release may diminish with diabetes, ageing, or some other disease states. In addition, the number of vascular smooth muscle cells may be diminished by the ageing and/or diabetic process, such that sildenafil is insufficient to produce a clinical effect. Indeed, many diabetic men with ED do not respond well to this medication [36]. Likewise, the injection of exogenous VIP can induce erection in several animal species, including man. There are two recent reports of direct intracavernosal VIP treatment for ED; Dinsmore et al. [37] and Elkabir et al. [38] both reported that intracavernosal injection with VIP combined with phentolamine mesylate is a safe and effective means of treating male ED of primarily non-psychogenic cause. There was a response rate of 85% in diabetic men with ED [37].

There is no doubt that despite the advent of oral therapies and injection with exogenous VIP, there is room for improvement in the treatment of ED. Such opportunities exist on at least two levels. First, there is a need for more effective treatments for patients with moderate to severe ED, and second, every currently approved non-surgical treatment option for ED requires planning before intercourse. Gene therapy could restore ‘physiological’ erection to the normal endogenous signals, with no need for any other form of therapy.

Gene therapy treats a specific disease by introducing genes engineered to correct the dysfunction leading to the disease. It can be designed to replace a specific ‘mutant’ gene with a good copy, or to introduce a gene to overcome a specific pathophysiological disorder. In the case of ED, where the dysfunction is multifactorial, current and future strategies are primarily focused on neurotransmitters and smooth muscle. To date, various gene therapies have been investigated for treating ED, including inducible NOS [39,40], endothelial NOS [41,42], penile-expressed neuronal NOS [43], human smooth muscle maxi-K+ channel protein [18], calcitonin gene-related peptide [44], and brain-derived neurotrophic factor [45] gene therapy.

In the present study, we chose VIP because: (i) although it is one of the main neurotransmitters and neural co-mediators with NO of penile erection [5], there are no reports of its use in gene therapy for ED; and

<table>
<thead>
<tr>
<th>Group/subgroup</th>
<th>Mean (s) ICP, cmH2O</th>
<th>Mean (s) VIP expression in arteries of penis</th>
<th>Mean (s) VIP expression in arteries of liver</th>
<th>Mean (s) VIP expression in arteries of kidney</th>
<th>Mean (s) VIP expression in arteries of aorta</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (1 day)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>50.2 (8.4)</td>
<td>0.42 (0.09)</td>
<td>0.72 (0.45)</td>
<td>1.16 (0.10)</td>
<td>0.86 (0.39)</td>
</tr>
<tr>
<td>2</td>
<td>55.4 (9.3)</td>
<td>0.55 (0.15)</td>
<td>1.01 (0.36)</td>
<td>1.25 (0.06)</td>
<td>0.74 (0.45)</td>
</tr>
<tr>
<td>3</td>
<td>86.0 (17.4)*</td>
<td>1.19 (0.31)†</td>
<td>0.89 (0.28)</td>
<td>1.36 (0.45)</td>
<td>0.95 (0.72)</td>
</tr>
<tr>
<td>B (3 days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>59.6 (14.4)</td>
<td>0.52 (0.35)</td>
<td>1.17 (0.27)</td>
<td>1.54 (0.82)</td>
<td>0.47 (0.23)</td>
</tr>
<tr>
<td>2</td>
<td>59.4 (17.2)</td>
<td>0.47 (0.24)</td>
<td>1.35 (0.08)</td>
<td>0.89 (0.38)</td>
<td>0.66 (0.27)</td>
</tr>
<tr>
<td>3</td>
<td>85.8 (15.5)*</td>
<td>1.47 (0.48)†</td>
<td>1.24 (0.44)</td>
<td>1.18 (0.90)</td>
<td>0.82 (0.34)</td>
</tr>
<tr>
<td>C (7 days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>49.0 (9.0)</td>
<td>0.46 (0.23)</td>
<td>1.05 (0.29)</td>
<td>0.90 (0.48)</td>
<td>0.90 (0.48)</td>
</tr>
<tr>
<td>2</td>
<td>59.6 (25.6)</td>
<td>0.51 (0.20)</td>
<td>0.90 (0.16)</td>
<td>0.74 (0.28)</td>
<td>0.57 (0.35)</td>
</tr>
<tr>
<td>3</td>
<td>94.8 (11.6)*</td>
<td>1.07 (0.31)†</td>
<td>1.16 (0.31)</td>
<td>0.89 (0.27)</td>
<td>0.89 (0.27)</td>
</tr>
<tr>
<td>D (14 days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>53.2 (26.6)</td>
<td>0.54 (0.13)</td>
<td>0.84 (0.51)</td>
<td>1.06 (0.41)</td>
<td>1.01 (0.52)</td>
</tr>
<tr>
<td>2</td>
<td>53.8 (16.6)</td>
<td>0.49 (0.22)</td>
<td>1.04 (0.34)</td>
<td>1.01 (0.37)</td>
<td>0.74 (0.46)</td>
</tr>
<tr>
<td>3</td>
<td>82.8 (13.9)*</td>
<td>1.03 (0.44)†</td>
<td>0.95 (0.53)</td>
<td>1.04 (0.52)</td>
<td>0.87 (0.40)</td>
</tr>
</tbody>
</table>

*P < 0.05 for control vs VIP-treated rats; †Dunnett’s t-test; P < 0.05 between controls and VIP-treated groups.
(ii), as VIP levels are lower in patients with diabetes- and ageing-related ED, the study was designed to introduce the VIP gene to overcome ED, and thus explore a potential effective and long-lasting therapy for ED by addressing the physiology underlying erection, with no frequent injections. Briefly, the rationale of VIP for gene therapy is that over-expression of this important endogenous smooth muscle relaxant and vasodilator will assist in ameliorating the diminished erectile response characteristic of ED in many patients.

The preliminary results indicate that pcDNA3/VIP cDNA is easily incorporated and its expression sustained in diabetic rat corpus cavernosum in vivo; moreover, this prolonged up-regulation of VIP is capable of altering the physiologically relevant erectile response, as measured by a significant increase in the ICP after stimulation of the cavernosal nerve.

The penis is an ideal organ for gene therapy because it is an appendage and therefore easy to access. In addition, it communicates with the peripheral vascular system, drugs (and by inference, gene-therapy vectors) rarely escape into the systemic circulation. However, as the corpus cavernosum is highly perfused, as are the liver, kidney and other organs, materials injected into the corpora may still rapidly enter the venous circulation. So that other organs were unaffected, we occluded blood flow to the rat penis by ligating the base of the organ for 30 min. The occluded blood flow to the rat penis by ligation of the base of the organ for 30 min. The preliminary results show that the expression of VIP mRNA in the liver, kidney and abdominal aorta was not changed significantly after VIP gene transfer; VIP gene transfer to the penis may have no effects on these other organs.

As with all other in vivo gene-therapy approaches, the basic objectives of gene therapy for organic ED should include: (i) efficient delivery of a gene into the penis; (ii) strong expression of the protein without altering its site of expression, and activated only during sexual stimulation; (iii) no serious side-effects; and (iv) a long-term effect. The present results suggest that VIP cDNA is efficiently incorporated into corpus cavernosum, and that its expression is sustained for at least 2 weeks in the penis, and activated only during nerve-stimulation in vivo.

In conclusion, VIP gene transfer to the diabetic rat penis was successful, with a greater ICP response to electrostimulation of the cavernosal nerve, and without changing the expression of VIP in the liver, kidney and abdominal aorta wall. It seems reasonable to assume that transfection with VIP cDNA is a potentially promising and physiologically relevant strategy for treating diabetic ED, if necessary, combined with NOS gene therapy.

ACKNOWLEDGEMENTS
This study was supported by grants from The National Nature Science Foundation of China (No. 30240034).

CONFLICT OF INTEREST
None declared. Source of funding: National Nature Science Foundation of China (No. 30240034).

REFERENCES
polypeptide in rat corpus cavernosum. BJU Int 2000; 86: 133–7
21 Seftel AD, Vaziri ND, Ni Z et al. Advanced glycation end products in human penis: elevation in diabetic tissue, site of deposition, and possible effect through INOS or eNOS. Urology 1997; 50: 1016–26
29 Dixon AF, Kendrick KM, Blank MA, Bloom SR. Effects of tactile and electrical stimuli upon the release of vasoactive intestinal polypeptide in the mammalian penis. J Endocrinol 1984; 100: 249–52
38 Elkahbi JJ, Walker RMH, Williams G. Successful treatment of venogenic erectile dysfunction with vasoactive intestinal polypeptide and phenolamine mesylate. BJU Int 1999; 83: S51

Correspondence: Zhou-Jun Shen, Department of Urology, 1st Affiliated Hospital, Medical College of Zhejiang University, Hangzhou 310003, PR China. e-mail: shenji@zju.edu.cn

Abbreviations: ED, erectile dysfunction; NO(S), nitric oxide (synthase); STZ, streptozotocin; VIP, vasoactive intestinal polypeptide; ICP, intracavernosal pressure.
Assessment of microheterogeneity of blood flow in the rat urinary bladder by high-resolution digital radiography

TAKAHIRO KIMURA, TOKUNORI YAMAMOTO, ATSUSHI SONE, ATSUSHI TAKENAKA and MASATO FUJISAWA
Department of Urology, Kawasaki Medical School, Kurashiki, Japan
Accepted for publication 24 November 2004

OBJECTIVES
To assess high-resolution digital radiography for measuring blood flow and thus examine the microheterogeneity of bladder microcirculation in a rat model.

MATERIALS AND METHODS
Microheterogeneity of blood flow in both mucosa and detrusor muscle of eight anaesthetized rats was investigated using an imaging technique with very high spatial resolution (0.1 x 0.1 mm²) using digital radiography combined with the deposition of ³H-labelled desmethylimipramine. The spatial pattern of blood flow was quantified by the coefficient of variation of the regional flow (CV = SD/mean).

RESULTS
Muscle blood flow was less than mucous blood flow (muscle : mucosa, 2.9 : 5) in the empty bladder. In the muscle layer the blood flow distribution was more heterogeneous than that in the mucosa, with a mean (SD) CV in muscle and mucosa of 0.33 (0.033) and 0.16 (0.019), respectively [P < 0.001] at the capillary level.

CONCLUSION
There was a heterogeneous distribution of blood flow in the microcirculation to capillary vessels in the muscular layer, possibly reflecting a difference in dynamic blood flow of regional perfusion of the emptied bladder.

KEYWORDS
bladder, radioactive molecular flow tracer, microcirculation, flow heterogeneity

INTRODUCTION
There are several studies of the relationship between bladder dysfunction and blood flow [1,2], with a heterogeneous distribution of blood flow in the bladder, and large differences in blood flow between the muscular and mucosal layers reported [3–6]. The relationship between bladder dysfunction and blood flow has also been recognised. Blood flow patterns in the bladder have conventionally been examined at a spatial resolution of several millimetres, but the microcirculation cannot be measured at such resolution. Thus the distribution of local blood flow in each of the muscular and mucosal layers has not yet been clarified.

In the present study we used a method for imaging the microcirculation in cardiac muscles and applied it to imaging the blood flow in the bladder wall [7], obtaining the distribution at a much higher spatial resolution (0.1 x 0.1 mm) than previously reported, using H-labelled desmethylimipramine (⁴H-DMI), as a blood flow tracer. Using this method we evaluated the heterogeneity of blood flow (microcirculation) in the muscular and mucosal layers of bladder separately.

MATERIALS AND METHODS
Eight male Wistar rats (8 weeks old) were intra-abdominally administered 30 mg/kg pentobarbital, artificially ventilated after tracheostomy, the bladder exposed by a median incision of the lower abdomen, and then emptied by cannulation from the top of the bladder. The heart was exposed by a median incision of the breast bone; a cannula was inserted for sampling arterial blood and measuring blood pressure. After the stability of cardiac function was confirmed by monitoring blood pressure, 2.2 MBq of blood flow tracer (⁴H-DMI) was injected into the left ventricle. One minute after the injection the heart was stopped by administering KCl to the left ventricle, and the bladder excised and stored in a freezer at −80 °C. Serial coronal sections (10 μm) of the bladder from the neck to the top were cut at −25 °C using a cryostat, spread on a glass slide and dried.

As ⁴H-DMI administered to the left ventricle is taken up in the bladder wall and binds to α2-receptors in endothelial cells in capillary vessels, α-irradiation activity increases with high densities of blood flow. The α-irradiation activity was detected using an ultra-high sensitivity radiation energy sensor (imaging plate, TR2040, Fuji Co., Tokyo, Japan). This plate has a 100-fold higher sensitivity for detecting radiation than conventional X-ray film, and detects and visualizes radioactivity over a wide dynamic range, with good linearity, high resolution and accuracy within a short time (Fig. 1). To minimize the effects of environmental radiation the bladder sections were placed in contact with the imaging plate for 3 days in a lead-shielded box. Analogue images of the distribution of activity of α-irradiation released from the plate were converted into digital signals at a resolution of 0.1 x 0.1 mm²/pixel by linear transformation using a bioimaging analyser (HGE, Fuji; Fig. 2B). As the intensity of α-irradiation activity was linearly transformed into a grey scale, and as the concentration corresponded to the distribution of blood flow, the region of interest (ROI) of each muscular and mucosal layer was traced (Fig. 2B) based on the submacro images corresponding to each image, and analysed (Fig. 2A). The variable for assessing the heterogeneity of the distribution of blood flow was the coefficient determined by dividing the SD of the grey scale values in the traced ROI by the mean, i.e. the coefficient of variation (CV) of local blood flow. The intensity of α-irradiation activity and the CV of local blood flow were then calculated.
blood flow between the muscular and mucosal layers, and between the serial top and neck sections of the bladder wall were analysed using Student’s t-test.

RESULTS

In all eight rats examined the mean (SD) intensity of α-radiation activity was 497 (21) in the mucosal and 282 (17) in the muscular layer, giving a ratio of 5 : 2.9. Direct comparison of the blood flow showed that the intensity of α-radiation activity was significantly higher (1.8-fold) in the mucosal than in the muscular layer ($P < 0.001$). The blood flow in the bladder was slightly higher in the neck region than in the top region (Fig. 3), with the serial sections of the top and neck regions of the bladder wall indicating significantly higher flow in the neck region of both muscular and mucosal layers than in the top region, at 275 (22) vs 301 (22) ($P = 0.007$) and 476 (18) vs 492 (9) ($P = 0.010$), respectively.

The heterogeneity of the distribution of blood flow in the muscular and mucosal layers, expressed as the mean (SD) CV, was 0.33 (0.033) in the muscular and 0.16 (0.019) in the mucosal layer, being significantly higher (about twice) in the former than in the latter, indicating greater heterogeneity of blood flow in the muscular layer ($P < 0.001$).

DISCUSSION

Since the first report by Nemeth et al. [8] in 1977, the distribution of blood flow in the bladder has been measured using the microsphere method, but as the spatial resolution of this method is limited to 3–8 mm because smaller blood vessels become obstructed, evaluating the microcirculation is impossible in this way. In the present study, blood flow in the bladder was imaged at ~60 times higher resolution (100 μm) than with the conventional method, and the heterogeneity of the distribution of blood flow in the mucosal and muscular layers was evaluated for the first time. The blood flow tracer ($^3$H-DMI) mostly binds to α2-receptors in endothelial cells in capillary vessels, and its usefulness for analysing microcirculation has been confirmed in cardiac muscles [7]. We applied this method to evaluate microcirculation in the bladder, which is a luminal organ with contractile function, like the heart.

The results indicate that blood flow in the mucosal was significantly higher than in the muscular layer. Previous studies reported the same difference in blood flow, with a ratio of 2 : 1 to 13 : 12 [8,9]. This may have been caused by microcirculation disorders induced by vascular obstruction, which is a disadvantage of the conventional microsphere method. As >98% of the $^3$H-DMI used in the present study binds to α2-receptors in endothelial cells in capillary vessels, the results are stable, with no artefacts caused by vascular obstruction and reduced resolution by diffusion to other tissues, as occurs with other molecular flow tracers. The evaluation of blood flow in serial sections prepared from the neck to the top of the bladder indicated that it was significantly higher in the former than in the latter. This was considered to be caused by differences in the density of blood microvessels within the vascular network in the bladder.

We confirmed the heterogeneity of the distribution of blood flow in the mucosal and muscular layers, and between the serial top and neck sections of the bladder wall were analysed using Student’s t-test.

FIG. 1. The sensitivity of the imaging plate (red) compared with conventional X-ray film (green).

FIG. 2. (A) A submacro image of the bladder wall, and (B), a digital radiogram of blood flow distribution in the bladder wall.

FIG. 3. The change in blood flow from the dome to the neck of the bladder for the mucosal (red) and muscle (green) layers.
muscular layer, using the higher resolution of the present method, with a significantly higher CV of blood flow in the muscular than in the mucosal layer, i.e. greater heterogeneity. The heterogeneity is affected by blood-flow regulation of the network structure of blood vessels, mechanical stimulation by expansion and contraction of the bladder wall, and changes in the arterial tone corresponding to local metabolism. Schroder et al. [6] produced chronic BOO in rabbits, measured the blood flow in the bladder, and reported that in the mucosa it was increased through loading on the bladder by BOO, up to a certain level, but continuously decreased in the muscular layer. This suggested that the difference in the heterogeneity of blood flow between the mucosal and muscular layers in the present study might be caused by mechanical stimulation and changes in the arterial tone. Stress on the bladder wall probably induced the proliferation of fibres in the interstitial tissues, which excluded blood vessels, and consequently caused local ischaemia. This induced micro-ischaemia-enhanced fibrogenesis of the muscular layer, resulting in reduced bladder compliance. However, as fibres do not exist in the mucosal layer, ischaemia is unlikely to create the same stress as in the muscular layer. Levin et al. [10] reported that the in vitro reactivity to ischaemia was higher in the mucosal than in the muscular layer. Furthermore, as blood flow is lower in the muscular than in the mucosal layer, the inhibition of blood flow in capillary vessels by haemocytes may be higher in the former than the latter, suggesting that the distribution of blood flow is more heterogeneous, as a result of the reduced density of functional capillary vessels. There is a significant difference in bladder microcirculation between the empty and full bladder.

Hohlbrugger et al. [11] reported on the autoregulation of vesical circulation in the human full bladder, using Doppler ultrasonography. In future work we will clarify the heterogeneity of blood flow in the full bladder at the microvascular level using the present method.

In conclusion, we examined blood flow patterns at a much higher resolution than conventional methods allow, using a molecular flow tracer that is selectively accumulated by endothelial cells in capillary vessels of the bladder wall. The distribution of blood flow in the microcirculation to capillary vessels was more heterogeneous in the muscular than in the mucosal layer. This technique will be helpful to clarify physiological changes in the blood supply of the bladder in various disease states.

CONFLICT OF INTEREST
None declared.

REFERENCES

Correspondence: Masato Fujisawa, Department of Urology, Kawasaki Medical School, 577 Matsushima, Kurashiki, 701–0192, Japan.
E-mail: masato@med.kawasaki-m.ac.jp

Abbreviations: *H–DMI, H*1-labelled desmethylimipramine; CV, coefficient of variation.
Back to the future for urological drug development?

Over the last few years several long-term studies, by design or accident, have had a potentially negative impact on the future of urological and andrological drug research and development. The more positive of these have included the Medical Treatment Of Prostatic Symptoms, which ultimately showed that either 5α-reductase inhibitor (finasteride) or α-blocker (doxazosin) therapy was good as monotherapy but also offered advantages (apart from cost perhaps) when used in combination. It is not known whether this has any actual impact on the extent of the co-administration of these drugs in the real world. Initially, the results with finasteride from the Prostate Cancer Prevention Trial were more equivocal, showing a lower incidence of prostate carcinoma but apparently a higher grade when manifest. However, it now appears that the latter is artefactual and the data augers well for the use of finasteride, at least in preventing prostate cancer. It remains to be seen what the outcome of a similar study involving GSK’s dutasteride will be in terms of both efficacy and artefact.

Unfortunately, perceptions can be difficult to dislodge. At the turn of the millennium the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial had a substantial impact on the considerable cardiovascular sales of doxazosin, it was subsequently realised that the change in perception arose from the trial design, however, the damage to patient and physician confidence was remarkably difficult to reverse. Although, it should have resulted in little change in the management of patients with BPH, there was a considerable decrease in prescriptions for this indication for over 2 years.

More recently, several long-term studies have led to a loss of confidence in the safety of at least one statin (cerivastatin) and several cyclooxygenase (COX) inhibitors, to an extent where stock prices have been substantially reduced as products have been withdrawn, and warnings in product labels have been strengthened. The impact of such post-marketing studies is already going beyond the primary therapeutic indication of the affected drugs.

In the context of urological and andrological drug development, the consequence of post-marketing long-term follow-up is already well documented. The clinical data resulting in contraindications and warnings for phosphodiesterase inhibitors with α-blockers only became apparent almost 5 years after the prototype (sildenafil) reached the market place. There is good evidence that FDA are increasingly interested in the safety aspects of novel chemical entities (NCEs). The re-filed NDA for Uprima by TAP was rejected as much for cardiovascular safety concerns as for any other reasons. It is likewise assumed that the Proctor and Gamble testosterone patch for women with hypoactive sexual desire disorder was rejected on a similar basis. The recent events in the COX-2 field can only have made the FDA even more conservative. Will this have any impact on the future of urological drug discovery and development? Unfortunately the answer is almost certainly yes.

In general urology deals with diseases that are not life-threatening (apart from cancers), and sexual medicine is associated with ‘lifestyle drugs’, at least in the eyes of the regulators and pricing authorities. As Lilly have found with duloxetine, which is under review both
as an antidepressant and for treating stress incontinence, the regulators can require different benefit-risk ratios for approval in each indication.

It is possible that the regulatory authorities could mandate more extensive (i.e. longer term) safety data before approval, rather than the existing post-marketing follow-up. For most chronic-use drugs this would not be commercially viable. It has been calculated that an additional 1 year to the whole phase III programme would increase the cost to the company by almost 75%. In this era of pricing restriction and competition from generics at an early stage, several poorly served urological diseases, e.g. stress incontinence and ejaculatory function, would become borderline viable, and interstitial cystitis and prostatitis would be excluded completely.

The picture for on-demand drugs is more optimistic, where the scale of long-term safety testing, e.g. for J&J’s selective serotonin re-uptake inhibitor (SSRI) dapoxetine for premature ejaculation may be less exacting but no less meaningful from the safety perspective. Dapoxetine appears to have a nearly ideal profile in this respect, as it is effective within an hour and has a short (but clinically useful) half-life of ~6 h. The ‘antidepressant’ SSRIs, which have been designed to give 24-h cover with much longer half-lives, would not have the advantage of such rapid clearance. Statistically, the average man has sex 49 times per year and on this basis, the requirement for long-term safety testing of an on-demand agent such as dapoxetine might be considerably relaxed.

Another way of reducing the possibility of an unexpected long-term side-effect is to develop only mechanistically similar or chemically similar NCEs. The latter option is seldom available as a tactic for a competitor these days because of the more effective and wider structuring of patent claims. However, terazosin and doxazosin are both structurally similar quinazolines, yet developed by different companies. The more viable strategy is the development of agents that are mechanistically similar, e.g. antimuscarinics and α-blockers. In addition, being slow to market is not necessarily a handicap; tamsulosin was the fifth α-blocker in most markets, yet gained and still retains >45% of the $2 billion BPH market, mainly because of an effective marketing strategy. Equally the second, third and fourth antimuscarinics to be marketed are likely to provide a better commercial return than the prototype, oxybutynin. The problem is that the overactive bladder and BPH markets are already reasonably well served, and the commercial returns for NCEs may be questionable.

So where does this leave urological/andrological drug discovery and development? Any chronic-use NCE for any field is going to be subject to ever-increasing regulatory hurdles, if it is for an indication that is ‘lifestyle’ or not life-threatening. On this basis, areas where a short-term risk-benefit ratio, e.g. urological cancers, would be particularly attractive. Equally, any situation where drugs could be used on demand or strategically, e.g. ejaculatory disorders or stress incontinence, would be viable. Perhaps in other areas, e.g. BPH and urinary urge incontinence, the only advances may be made by using combinations of existing agents.

Next month I will examine what the pharmaceutical industry is doing to identify new urological targets.
Modified tubularized transverse preputial island flap repair for severe proximal hypospadias

RAKESH P. PATEL, ASEEM R. SHUKLA, J. CHRISTOPHER AUSTIN and DOUGLAS A. CANNING
Division of Paediatric Urology, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA
Accepted for publication 15 November 2004

INDICATIONS

The best surgical approach for repairing proximal hypospadias with chordee remains controversial among urologists. Based on various considerations, from age and anatomy to surgeon preference, techniques have been described that might be broadly classified as single- or multiple-stage procedures. Numerous alternatives have been described for single-stage neourethral reconstruction for proximal hypospadias, including prepuce-based flaps, incised-plate urethroplasty, and free grafts, with varying results [1–4]. Surgical innovation has enabled most variants of hypospadias to be repaired with preservation of the urethral plate, but proximal hypospadias with severe chordee might still require transection of the urethral plate. Since Duckett [5] first described the transverse preputial island flap (TPIF) repair in 1980, we have continued to prefer to incorporate vascularized preputial flaps for these difficult cases.

The traditional TPIF creates the neourethra by tubularizing the dorsal preputial tissue into a neourethra and then transferring the tube to the native urethra proximally, and to the glans distally. This repair has a complication rate of 32–42% in some reports [6–8]. In our experience there were complications after repair, especially urethral diverticula and meatal stenosis, in a few boys when the meatal opening or penis was small, or when the chordee was severe. Recently, we developed a modification of the Duckett TPIF that uses one side of the island flap to recreate a urethral plate, with the remainder of the flap being tailored and rolled to recreate a neourethra. This modification makes it easier to tailor the urethroplasty appropriately to create a more consistent neourethra with less risk of diverticulum and stenosis. We consider that reducing the likelihood of leaving redundant tissue in situ minimizes the risk of diverticulum formation, turbulent voiding and urethrocutaneous fistula. The purpose of this report is to share our technique and results.

METHODS

The TPIF is created as follows. A glans-holding suture is placed and a circumcising incision is outlined with a marker and extended on the midline to the penoscrotal junction. We think that proximal extension of the ventral incision facilitates subsequent harvesting of the onlay flap by allowing the penile shaft skin to flatten, resulting in better visibility of the pedicle of the flap, and better separation of the pedicle and the dorsal penile shaft skin. To ensure haemostasis, we infiltrate a solution of 1 : 100 000 noradrenaline and 1% lidocaine along the marked line. The skin is then incised and the penis degloved superficial to Buck's fascia, beginning the dissection ventrally,
from the urethral meatus to the penoscrotal junction, and then dorsally to the penopubic junction. The urethral meatus is incised proximally until vascularized corpora spongiosum of normal appearance is encountered, and normal bleeding from the native urethra is noted. An artificial erection is induced, and if the chordee is severe, the urethral plate is transected and dissected away from the corporal tissue until the tethering effect of the spongiosal tissue is released. The ventral dissection of the urethral plate sometimes results in a relatively distal urethra displaced to the penoscrotal junction or even to the perineum. The glans is deeply incised in the midline and excess epithelium trimmed. If required, dorsal longitudinal incisions of appropriate length are made off the midline and closed horizontally to correct chordee. The artificial erection is then repeated.

When the penis is straight, a segment of inner preputial tissue is harvested from the redundant dorsal prepuce, and the mesentery of the flap is buttonholed and ventrally transposed (Fig. 1a). The native urethral
meatus, which is now relocated more proximally, is fixed to the corpora cavernosa with fine absorbable monofilament sutures.

Previously we constructed the urethra from the island flap by rolling the tissue over a tube and then suturing the proximal end to the native urethral meatus at the penoscrotal junction or at the perineum [5]. We currently construct the urethra by first anchoring one side of the flap longitudinally to the ventral surface of the corpora cavernosa just to the right or left of the midline using 7–0 polyglactin sutures (Fig. 1b). The anchoring begins at the posterior wall of the native urethra and proceeds distally to the proposed location of the neomeatus in the glans. This creates a new urethral plate of inner preputial skin, which no longer binds the ventral corpora. The anchored medial edge of the tube allows the opposite end of the flap to be stretched to mark the redundant flap skin that can be discarded to construct an appropriately sized neourethra (Fig. 1c). The tube must be narrowed substantially at the proximal anastomosis between the new and spatulated native urethra to align the anastomosis properly, and to construct a tube of ideal calibre with no diverticulum at the distal extent of the native urethra. For most boys reconstructed in their first year, we use an 8 F feeding tube as a template to gauge the urethral lumen as the closure proceeds.

To construct the neourethra, a second interrupted subcuticular suture line is placed, adjacent to the first suture line, longitudinally along the ventral penile shaft (Fig. 1d). The urethral reconstruction continues proximally to the glans penis. A glansplasty is completed over an 8 F urethral stent with 6–0 absorbable monofilament horizontal mattress sutures placed parallel to the cut edge of the glands, to cover the distal edge of the tube and to provide an anatomically accurate appearance. The 8 F stent is exchanged for a 6 F stent that is left indwelling for 2–2.5 weeks, and dorsal preputial skin is fashioned to provide adequate skin coverage, as in all hypospadias repairs (Fig. 1e).

The repair is covered with a dressing that compresses the penis against the lower abdominal wall by placing a thin nonabsorbent pad and a folded gauze sponge on top of the penis, followed by a bio-occlusive dressing. Trimethoprim-sulphamethoxazole is provided as prophylaxis while the urethral stent remains in place.

Between 1997 and 2001, we performed 12 modified TPIF repairs on boys with penoscrotal or scrotal hypospadias with severe chordee. All of these repairs required transection of the urethral plate to resolve the penile curvature, and the mean (median, range) follow-up is now 24.5 (24, 20–33) months.

ADVANTAGES AND DISADVANTAGES

The ideal surgical correction for penoscrotal or perineoscrotal hypospadias with severe chordee remains elusive. In addition to allowing a single-stage repair with the attendant benefits to the patient, the primary advantage of the modified TPIF over free graft repairs is the incorporation of vascularized preputial flaps. We recently reported a 20-year review of outcomes using vascularized preputial flaps for severe hypospadias at our institution, that confirmed the long-term viability of these flaps [9]. Our preference continues to be to use preputial flaps as an island onlay when the urethral plate is preserved, or as an island tube when it is not [10]. Essentially, the modified TPIF converts a difficult procedure (the original TPIF) into a more commonly used and consistent island onlay repair, by recreating a urethral plate with one side of the ventrally transposed inner preputial skin that is anchored to the medial margin of the corpora. By anchoring the medial edge of the flap to the corpora, the opposite end of the flap can be stretched to match the neourethra accurately to the size of the native urethra. This minimizes formation of a urethral diverticulum where the native urethra meets the neourethra, and reduces the risk of turbulent voiding that might contribute to the formation of urethral diverticula. Furthermore, the adjacent suture lines are dorsal, which we think also minimizes the risk of fistula.

The primary limitation of this initial experience remains the relatively short follow-up compared to our institutional experience with the original Duckett TPIF, that now exceeds two decades. However, with a follow-up of at least 2 years for these 12 patients after the modified TPIF, we would have expected to encounter most complications by now. Our experience continues to increase with this technique, and we continue to carefully evaluate our results.

DIFFICULTIES AND COMPLICATIONS

Two of the 12 boys undergoing a TPIF repair developed a complication requiring surgical intervention; one developed a fistula and one was treated for meatal stenosis that caused proximal urethral ballooning. Excellent results, with a straight penis and voiding from a distal glanular meatus, were obtained in 11 boys. The final slit-like meatus was properly placed, with no fistulae, urethral diverticula, stenosis or persistent chordee in these boys. Separation of the glans wings in one boy will require an additional procedure for definitive repair.

This relatively simple modification of Duckett’s original description has resulted in a considerable reduction in our complication rate after these procedures. Although there were few patients, which reflects the few that we think require transection of the urethral plate with release of ventral tethering tissue, we consider that this modification will help others who have had similar difficulties with the traditional TPIF repair.

CONFLICT OF INTEREST

None declared.

REFERENCES

1 Snodgrass WT, Lorenzo A. Tubularized incised-plate urethroplasty for proximal hypospadias. BJU Int 2002; 89: 90–3
7 Dewan PA, Dinneen MD, Winkle D, Duffy PG, Ransley PG. Hypospadias:

**Correspondence:** Douglas A. Canning, Division of Paediatric Urology, Children’s Hospital of Philadelphia, 3rd Floor Wood Building, 34th Street and Civic Center Boulevard, Philadelphia, PA 19104–4399, USA.
e-mail: canning@email.chop.edu

**Abbreviations:** TPIF, transverse preputial island flap.
Tubeless and stentless percutaneous nephrolithotomy

VIKAS GUPTA, TRILOK C. SADASUKHI, KRISHAN K. SHARMA, RAM G. YADAV and RAJEEV MATHUR
Department of Urology, SMS Medical College and Hospital, Jaipur, India

Accepted for publication 29 November 2004

INDICATIONS

In 1955 Goodwin et al. [1] reported the use of percutaneous drainage in a patient with an obstructed kidney. Percutaneous nephrolithotomy (PCNL), as a primary procedure, was subsequently described by Fernstrom and Johanson in 1976 [2]. This technique is applicable to the removal of a wide variety of renal stones [3–5]. Modifications have been attempted to decrease the morbidity of the procedure, including the use of a smaller working sheath, termed the ‘mini-PCNL’ [6–8], and avoiding a nephrostomy tube completely with a JJ stent left for drainage of the urine after surgery, termed the ‘tubeless PCNL’ [9,10]. Here we describe our experience with PCNL in selected cases with no use of a nephrostomy tube or JJ stent after PCNL.

METHODS

Between August 2002 and July 2004, 1405 patients were treated with PCNL; in 96 selected patients no nephrostomy tube and no internal stenting was used afterward. Indications included a symptomatic stone in situ £ 1 cm with resistance to ESWL. The stone was considered resistant to ESWL if there was no fragmentation at the end of two sessions or no clearance after four. The inclusion criteria for the tubeless and stentless PCNL included the selected cases, where there was one puncture with no intraoperative complications, e.g. significant perforation of the collecting system and significant bleeding, complete stone clearance and a clear efflux.

The stone-bearing calyx was approached directly under fluoroscopy. No retrograde catheter or occlusion balloon was used. The nephrostomy tract was dilated to 24 F if the stone could not be fragmented by ESWL and to 16 F if the stone was fragmented by ESWL but could not be cleared. The stone was removed using two-prong forceps. The nephrostomy site was closed using #1 silk suture. A pain questionnaire (‘no pain’, ‘mild’, ‘moderate’, or ‘severe pain’) was given to the patient on the day after the operation to assess pain. No routine imaging was used to detect urinoma or haematoma when the recovery was uneventful. Patients were discharged when the urine was clear, there was no leaking from the wound site, and no pain, with subsequent follow-up at 3 weeks and 3 months.

The mean (range) age of patients was 32 (17–58) years. The male : female ratio was 3 : 2. The mean (range) operative duration was 18 (10–25) min, which included the time to obtain access to the desired calyx. The mean (range) duration of hospitalisation was 1.8 (1–5) days. The patients who had tubeless and stentless PCNL required substantially less analgesia than those who had the standard PCNL procedure. No patient required morphine. One patient required a transfusion of two units of blood for haematuria after surgery although there was no significant intraoperative bleeding. Haematuria settled by the third day after surgery and JJ stenting was used and the patient improved.

COMPARISON WITH OTHER METHODS

Most simple renal calculi can be treated satisfactorily with ESWL. Several factors are associated with poor results using ESWL, including stones within the dependant or obstructed portions of the collecting system, stone composition (mostly calcium oxalate monohydrate and brushite), obesity or a habitus that inhibits imaging and causes unsatisfactory targeting of the stone [11]. In 1992, Sampio and Aragao [12] emphasized the importance of lower calyceal anatomy for clearing stones. For the patient whose stone cannot be cleared by ESWL another treatment option must be used. The tubeless PCNL technique was developed in an attempt to remove renal stones with minimal morbidity, with a JJ stent used for urine drainage afterward. However, ureteric stenting increases morbidity, stent-related complications and is an additional cost.

In the present study we evaluated 96 patients treated with tubeless PCNL and no JJ stenting. The patients had a shorter hospital stay and less morbidity, primarily as a result of minimal instrumentation of the ureter and no ancillary procedures such as nephrostogram or stent removal. The benefits gained in terms of cost saving are substantial, as the cost of a nephrostomy tube, nephrostogram, a stent, and stent removal is completely negated. One patient in the present study required JJ stenting for substantial leaking from the PCNL site, which was thought to be caused by an undetected intraoperative perforation of the collecting system. Ultrasonography was unremarkable; JJ stenting was used and the patient improved.

The hospitalisation in the present study was 1.8 days, longer than in some recent studies with standard tubeless PCNL. We discharged the present patients when there was no leaking from the PCNL site and the urine was clear, which might have added a few extra hours.

The tubeless and stentless PCNL is safe, offering substantial advantages in morbidity and cost-effectiveness when compared with standard tubeless PCNL techniques, and should be considered as an option for managing renal calculi in selected patients.

CONFLICT OF INTEREST

None declared.

REFERENCES

1 Goodwin WE, Casey WC, Woolf W. Percutaneous trocar [needle] nephrostomy in hydronephrosis. JAMA 1955; 157: 891–4
5 Elder JS, Gibbons RP, Bush WH. Ultrasonic lithotripsy of a large staghorn calculus. J Urol 1984; 131: 1152–4

Correspondence: Vikas Gupta, Department of Urology, SMS Hospital, Jaipur, India. e-mail: pnhiuka@indiatimes.com

Abbreviations: PCNL, percutaneous nephrolithotomy.
THE MOLECULAR STAGING OF PROSTATE CANCER

Sir,

In their review of current and emerging approaches to extraprostatic prostate cell detection [1] McIntyre et al. concentrate on RT-PCR, Immunocytochemistry, an alternative which they mention, has been augmented by automation and offers rapid processing of many samples, visualisation of circulating tumour cells and interrogation of their genotype.

Automated immunofluorescence microscopy was initially developed to allow noninvasive prenatal diagnosis [2]; preparations of maternal blood on microscope slides could be scanned, signals from fluorescently labelled fetal-specific antibodies identified, fetal nucleated red blood cells and FISH of individual cells could be used to detect polysomy. This technique has been adapted for investigating cancer. After enriching blood samples by density-gradient centrifugation, fluorescently labelled antibodies to antigens overexpressed in epithelial tumours [3,4] or specifically by prostatic cells (e.g. PSA and PSMA) are used to highlight cells for further analysis. FISH (where individual chromosomes or DNA sequences are fluorescently labelled) can detect aneuploidy or even the amplification of a specific gene within a circulating tumour cell. This technique gives a better estimate of the number of tumour cells in blood; to obtain such information using RT-PCR would require an assessment of the amount of mRNA per cell and its survival through the isolation process.

Escape of cells into the circulation seems to be an early event in the development of prostate cancer [5] and its detection is not necessarily a surrogate marker of metastatic disease. When genetic changes associated with the acquisition of the capacity for establishing distant deposits have been identified, circulating cell detection will make a useful contribution to the molecular staging of prostate cancer.

GEORGE YARDY, STEPHEN McGREGOR and SIR WALTER BODMER
Cancer & Immunogenetics Laboratory, Weatherall Institute of Molecular Medicine, John Radcliffe Hospital, Oxford,


PROSTATE SIZE INFLUENCES THE OUTCOME AFTER PRESENTING WITH ACUTE URINARY RETENTION

Sir,

I was a little surprised to see this letter [1] published without being given an opportunity to respond to the criticism it makes of our paper [2]. Perhaps the BJU International policy regarding correspondence has changed, but if letters about papers are to be published without the corresponding author having an opportunity to respond, then there must be alternative ways of verifying the content of such letters. Although I have no desire to become involved in an unedifying or personalised correspondence, I feel that I must highlight and redress the factual inaccuracies contained in this letter.

In our study we concluded that men with large prostates on a DRE were more likely to have recurrent acute urinary retention (AUR) or require surgery within a 6-year period of follow-up after a successful trial without catheter (TWOC) after presenting with a first episode of AUR. We recognise that assessment by a DRE limited the value of the study, as did the relatively few patients included [34]. However, this finding was supported by data from the ALFAUR study, showing that a higher PSA level (measured 1 month after a successful TWOC, as a surrogate of prostate volume) is associated with a greater failure rate in the 6 months after a successful TWOC [3].

I acknowledge that it is entirely reasonable to criticise our study on the basis that, as the study was conducted in four centres, several observers were assessing the prostate volume by DRE. However, these observers were only asked to state whether the prostate felt small, medium or large. Consequently, the effect of inter-observer error on our conclusion should be minimal, as there is evidence that assessing prostate size by a DRE tends to underestimate the volume of the prostate compared with a TRUS measurement [4]. It could be reasonably concluded that when a prostate feels large, then it is.

In Irwin’s study the prostate volume of 40 patients presenting with ‘AUR’ (retention volumes 500–2800 mL, six with a history of TURP) had their prostate volume assessed by a DRE by one experienced urologist. The finding that those who had a successful TWOC had a mean prostate volume of 15.9 mL, whilst in those who failed to void it was 27.5 mL, was statistically significant when tested using
the chi-squared test, and resulted in the conclusion that prostate volume influenced the outcome of a TWOC. The follow-up was continued to 2 years but no data were presented on the factors that may have influenced longer-term outcome [5].

I trust that a careful reader will agree that these two studies are neither identical nor are the conclusions reached the same. Although the conclusion reached by Kumar et al [5], that prostate size influences the outcome of a TWOC, may be proved to be correct, there are several reasons why I believe that this conclusion cannot be substantiated by the data they presented [6]. In view of this, and the longer-term nature of our study, we did not feel that it was necessary, or entirely appropriate, to cite the paper by Kumar et al [5].

ALAN McNEILL, Consultant Urological Surgeon, Western General Hospital, Edinburgh, UK

1 Irwin PP. Prostate size influences the outcome after presenting with acute urinary retention. BJU Int 2005; 95: 190
2 McNeill SA, Rizvi S, Byrne D. Prostate size influences the outcome after presenting with acute urinary retention. BJU Int 2004; 94: 559–62
4 Roehrborn CG. Accurate determination of prostate size via digital rectal examination and transrectal ultrasound. Urology 1998; 51: 19–22

ROBOTICALLY ASSISTED SURGERY

Sir,

The last two editions of the BJU International contained four articles on robotic surgery [1–4] and a cover figure of advertising material for the da Vinci robot system. Most readers will draw the conclusion that they too must obtain a surgical robot to stay ‘in the game’, and that they can safely skip the awkward intermediate step of laparoscopy. Having done 500 radical prostatectomies in the past 6 years using open, laparoscopic and robotic surgery I feel well placed to indicate some of the problems inherent in this approach.

The dictionary definition of a robot is ‘a machine capable of carrying out a series of complex series of actions automatically’ [5]. Thus the ingenious da Vinci device is not really a robot, because it does nothing automatically. Rather, it is a computerized master-slave interface. Someone still needs to do the operation, and they are heavily reliant on the enthusiasm, skill and co-operation of the assistant, who stands at the operating table several feet distant from the surgeon. Needless to say, the surgeon is also totally reliant on the correct functioning of the complex piece of equipment between he or she and the patient. If either of these components fails the approach needs to be abandoned and the procedure completed by open surgery. This is because the manual and problem-solving skills needed to perform advanced laparoscopic procedures, especially radical prostatectomy, are very different to the skill set needed to perform the same procedure sitting at a computer console. This is the crucial weakness of robotic surgery; it does not allow the operator to learn laparoscopic surgery. It therefore needs to be viewed as a competitor to laparoscopy rather than an aid to mastering it. The Australian Safety and Efficacy Register of New Interventional Procedures review of robotic surgery is the only independent assessment of the subject, and indicates several other problems which have receive little or no exposure in publications on robotic surgery, i.e. the need to train the whole theatre team, limited instrumentation, technical malfunctions and collision of the robotic arms, and a life-expectancy for the system of only 5 years (http://www.surgeons.org/ aernip-s/publications_robotics.htm).

Many publications show that in expert hands oncological and functional outcomes are similar after open and laparoscopic urological surgery. The generic advantages of laparoscopy and reduced bleeding are the reasons which make this a more appealing choice for both patient and surgeon. There is now a general consensus that laparoscopic surgery will replace most of the major urological procedures traditionally done by open surgery. Heads of department presently undecided about whether to embark on the laparoscopic or robotic pathway should consider two important points. First, the purchase and running costs of a da Vinci robot for a year could be used instead to provide a 1-year laparoscopic Fellowship for 18 urologists, who could then use the skills acquired to benefit patients for the rest of their professional careers, or 18 000 h of training in a ‘wet lab’. Second, those bodies responsible for healthcare reimbursement are not likely to agree to purchase two procedures for the same condition, with identical benefits and outcomes but with vastly differing costs [6].

The wave of euphoria surrounding robotic surgery, generated more by the manufacturers’ marketing than by fact, threatens to overshadow possibly the most important non-clinical problem facing urologists in 2005, i.e. how to address the significant imbalance between the supply and demand for training in laparoscopic urology. Caught between the nay-sayers of laparoscopy and the laparoscopic ‘experts’ who have a vested interest in limiting the diffusion of laparoscopic skills, are very many trainees whose needs are not currently being met. This problem can only be solved at a national level, but there are too few examples (Belgium and Scandinavia are exceptions) of national bodies taking appropriate steps to address this issue. This needs to change.

CHRISTOPHER G. EDEN, Department of Urology, North Hampshire Hospital, Basingstoke, Hants, UK

1 Peters CA. Robotic-assisted paediatric pyeloplasty: cutting edge or expensive toy? BJU Int 2004; 93: 1214–5
2 Herrell SD, Smith JA Jr. Laparoscopic and robotic radical prostatectomy: what are the real advantages? BJU Int 2005; 95: 3–4
4 Sundaram CP, Koch MO, Gardner T, Bernie JE. Utility of the fourth arm to facilitate robot-assisted laparoscopic radical prostatectomy. BJU International 2005, 183–6
5 Swannell J ed. Oxford Modern English
SACRAL RATIO AND FECAL CONTINENCE IN CHILDREN WITH ANORECTAL MALFORMATION

Sir, We read with interest this article [1] about the sacral ratio and fecal continence in children with anorectal malformation (ARM). In the study, the sacral ratio was reported as being of no practical value in identifying patients likely to have fecal incontinence. However, some points about the patients are not clear. The type of the ARM and continence criteria should be defined more detailed. It is known that type of the ARM is an important prognostic factor for continence in patients with ARM [2]. In routine clinical practice there are scoring systems for assessing fecal continence; the Kelly scoring system (KSS) and Kiesewetter-Chang (KCSS) are the most common and accepted for evaluating the continence level. According to the KSS the results are classified as good (5–6 points), fair (3–4) and poor (1–2), considering the frequency of bowel movements, stool consistency, soiling, sensation, feeling of fullness, the warning period, and the need for care. According to KCSS system patients are classified as good (continent), fair (socially continent) and poor (incontinent) [3,4].

We conducted a study for assessing the continence level in intermediate and high level ARM. Between September 1994 and May 2001, 17 patients with intermediate and 11 with a high-level ARM were operated in our clinic, all by the same surgeon and the same technique. In this series we investigated the continence status by the KSS and KCSS, the sacral ratio and by anorectal manometry. The Pearson correlation test and chi-squared test were used to assess the results. There was a significant correlation between the sacral ratio and continence score ($r = 0.548$, $P < 0.01$), and the clinical results were supported by anorectal manometry. In the good continence group the mean (SD) anal resting pressure was significantly higher than in the fair and poor groups, at 57.9 (8.57) and 32 (12.8) cmH$_2$O, respectively.

Pena [2] reported that the sacral ratio was a prognostic factor for continence in ARM; we agree, and routinely use the sacral ratio, KSS, KCSS and anorectal manometry for evaluating the prognosis of the continence level in patients with ARM. The differences between the results of Macedo et al. and those presented here might be attributed to the differences in patient assessment for continence and classification of the ARMs.

SUZI DEMIRBAG*, EMRE SENEL†, SALIH CETINKURSAN*,
*Gulhane Military Medical Academy, Pediatric Surgery, Ankara, Turkey, and †SSI Children Hospital, Pediatric Surgery, Ankara, Turkey


COMPARATIVE STUDY OF DARTOS FASCIA AND TUNICA VAGINALIS PEDICLE WRAP FOR THE TBULARIZED INCISED PLATE IN PRIMARY HYOSPADIAS REPAIR

Sir, I read with interest this paper [1]; the authors described a prospective comparison of two techniques of neourethral cover after tubularized incised plate (TIP) urethroplasty, and their results seem to indicate that one technique was better than the other. However, I make the following comments.

There is no indication in the report that the two groups were randomized, and there were significantly different numbers of patients in the two groups. What were the selection or inclusion criteria in each group and for inclusion into the study as a whole? The operative procedures seem to have been performed by an array of surgeons from different institutes. It is well known that appropriate patient selection is a key factor in the success of any hypospadias surgery, as are the skills of the individual surgeon. There is no indication in the report that these areas of potential bias were addressed. For example, poorly formed urethral plates are unsuitable to the TIP technique and can give poor results.

The authors report a fistula rate of 15–20% for TIP with a dartos fascia cover. Considering that most of their cases were of anterior or midpenile variety of hypospadias, this fistula rate is unusually high.
rate is rather high. Many earlier reports, some of them multi-institutional studies with many patients, reported much lower fistula rates (as low as 1%) using a TIP repair with dartos cover [2,3]. In other reports, when TIP with a dartos flap was used for proximal hypospadias repair, the fistula rates were still reasonably low [4]. How can the authors of the present study explain their poor results in the group having a TIP with dartos fascia?

Apart from selection bias, the high fistula rate in the present series could be attributable to ignoring the basic principles of hypospadias surgery, e.g. the use of optical magnification and fine instrumentation, apparently not adopted by the authors. Do the authors recommend that hypospadias repairs be undertaken by amateur surgeons without the use of the refined techniques of magnification and fine instrumentation?

I agree that dissecting a tunica vaginalis flap is not a difficult task, but my policy has been to use it while repairing severe hypospadias (where the dartos fascia has been used for vascularized skin flaps) and in salvage hypospadias repairs. It is not the first choice in my institution of tissue for neourethral cover in primary and especially distal hypospadias repair. A literature search also reveals that the principal uses of tunica vaginalis are in re-operative and salvage hypospadias repairs, e.g. [5].

In primary TIP urethroplasty, the dorsal subcutaneous (dartos) fascia is intact, abundant, easy to mobilize and can cover the neourethral suture line even down to the penoscrotal junction. Thus, it should be the logical choice for neourethral cover after primary TIP repair. Another very useful additional cover for the neourethra is corpus spongiosum. When mobilized on both sides of the urethral plate and sutured in the midline, it can provide additional protection for the neourethra. My personal experience with its use as an adjunct for TIP urethroplasty has been very gratifying, and spongioplasty can be combined with dartos flap cover for additional protection.

Separating the processus vaginalis from the spermatic cord is not without complications, especially in a small child. For example, both the vas and testicular vessels are at risk of injury during inguinal hernia repairs in children [6]. Is it reasonable to expose a child with virgin distal hypospadias to this risk, however low it may be, when alternative, reliable, safe and time-tested techniques are available? Nevertheless, I congratulate the authors on this interesting study.

VEMURI V.S.S. CHANDRASEKHARAM, Department of Paediatric Surgery & Paediatric Urology, Rainbow Children’s Hospital, Hyderabad, Andhra Pradesh, India

1 Chatterjee US, Mandal MK, Basu S, Das R, Majhi T. Comparative study of dartos fascia and tunica vaginalis pedicle wrap for the tubularized incised plate in primary hypospadias repair. BJU Int 2004; 94: 1102–4
4 Chen SC, Yang SS, Hsieh CH, Chen YT. Tubularized incised plate urethroplasty for proximal hypospadias. BJU Int 2000; 86: 1050–3
Surgery Illustrated

Surgical Atlas

Radical retropubic prostatectomy: apical preparation and curtain dissection of the neurovascular bundle

WOLFGANG HORNINGER, HANNES STRASSER and GEORG BARTSCH
Medical University of Innsbruck, Department of Urology, Innsbruck, Austria

ILLUSTRATIONS by STEPHAN SPITZER, www.spitzer-illustration.com

PATIENT SELECTION AND INDICATION
Radical prostatectomy should be reserved for men diagnosed with localized prostate cancer with a total PSA level of <15 ng/mL who are likely to be cured and have a life-expectancy of ≥10 years. Surgery is deferred for ≥2 months after prostate biopsy and for 3 months after TURP. This delay enables inflammation or haematoma to resolve so that the anatomical relationships between the prostate and the surrounding tissue return to a near-normal state.

PATIENT PREPARATION
Patients are admitted to the hospital 1 day before surgery, and blood and urine samples are assessed; in the afternoon patients are shaved and receive one colonic enema. On the day of surgery patients wear compression stockings.

SPECIAL INSTRUMENTS
Radical retropubic prostatectomy requires few special instruments. A headlight and magnifying loupes are very useful for the procedure, especially for a sufficient nerve-sparing procedure. We use a standard Balfour retractor to provide cranial and posterior retraction on the peritoneum and bladder. A right-angle clamp (Scott McDougal), a coagulating forceps and small clips are the only special instruments that should be available.
The patient is placed in a hyperextended supine position to increase the distance from the umbilicus to the symphysis, supplemented by a mild Trendelenburg position.

The skin incision is a lower abdominal midline incision and starts above the symphysis and extends upwards for some centimetres below the umbilicus. Antibiotic prophylaxis with amoxicillin is started during surgery, and subcutaneous prophylaxis for deep vein thrombosis on the evening of the same day.
Figures 2 and 3

After incising the endopelvic fascia the anterior aspect of the prostate is dissected free of fatty tissue, and the superficial branch of the deep dorsal penile vein dissected. Then the puboprostatic ligaments are cut and the dorsal vein complex under-run and ligated.
Subsequently, the anterior surface of the membranous urethra is incised ≈2 mm anterior to the apex of the prostate. The first anastomotic suture (poliglecaprone 2/0, double-armed UR-6 needle) is passed at the 1 o’clock position, taking care not to include the rhabdosphincter but only the urethra. The second anastomotic suture is passed in the same fashion at the 11 o’clock position.
By alternately pulling the catheter to the left and right with a forceps, the third and fourth anastomotic sutures are passed at 3 and 9 o'clock positions, respectively, also taking care not to include the rhabdosphincter or the neurovascular bundle in the suture.
The nerve-sparing approach is then attempted; the prostate is first pushed to the left or to the right below the bladder neck so that the lateral pelvic fascia can be incised. Using magnifying lenses, dissection of the neurovascular bundles starts very far anteriorly to preserve all the nerve fibres that are spread out concavely as described ('bob run' or 'curtain' shape) along the surface of the lobes of the prostate (Fig. 7a). With this type of preparation the vast majority of cavernosal nerves forming the neurovascular bundles can be preserved. The neurovascular bundles are teased away to the distal third of the prostate.

Figure 7

a (correct)

b (incorrect)
Figure 8

The posterior surface of the urethra and the underlying perineal body are then dissected. As most of the cavernosal nerves are situated dorsolateral to the membranous urethra at no time is the urethra under-run with a clamp. Subsequently, the apex of the prostate is dissected from the neurovascular bundle and the rectal fascia. After cutting half of the posterior surface of the urethra a traction suture is placed at the 6 o’clock position.
Pulling on this traction suture facilitates placing the fifth anastomotic suture line at the 5 o’clock position and medial to the neurovascular bundle. The sixth anastomotic suture line is passed in a similar fashion at the 7 o’clock position.
After removing the surgical specimen on both sides of the rectum the neurovascular bundles are visible; the previously placed urethral sutures are passed through the vesical neck at the corresponding positions and tied over a 20 F urethral catheter to complete the vesico-urethral anastomosis.
ANATOMICAL CONSIDERATIONS OF THE CAVERNOSAL NERVES

According to anatomical studies in 29 male fetuses, at our institution, the original course of the cavernosal nerves could be detected during the early stages of fetal development, as the prostate does not start to develop before fetal week 13. Because there is no prostate and the nervous structures are relatively thick, the cavernosal nerves were visible running downward lateral and dorsal to the prostatic and the membranous urethra, and the omega-shaped rhabdosphincter, which covered the ventrolateral aspects of the prostatic and membranous urethra between the bulb of the penis and the bladder neck.

After 13 weeks of gestation the prostate begins to develop. Because of the growth and increasing volume of the prostate, the course of the cavernosal nerves begins to change. By contrast, the prostate increasingly displaces the cavernosal nerves dorsolaterally. In this region the nerve fibres and vessels are increasingly dispersed along the convex surface of the prostatic capsule. Therefore, the cavernosal nerves running in the neurovascular bundles increasingly assume a shape that can best be compared to the concave ‘steep turn of a bob-sleigh run’ or a concave ‘curtain’ covering both prostatic lobes. At the apex of the prostate the nerve fibres of the neurovascular bundles converge again, like the exit of a steep turn of a bob-sleigh run, and lie adjacent to the membranous urethra. According to these anatomical findings, the modified apical preparation and the dissection of the neurovascular bundle is described and illustrated.

POSTOPERATIVE MANAGEMENT

Drains are routinely removed 3 days after surgery; the diet is advanced as tolerated, with normal intake by 3 days in most patients. Antibiotic prophylaxis with amoxicillin continues after surgery until the catheter is removed. On the 10th day gravity cystography is used under fluoroscopic control. The bladder is filled with 150–250 mL of a contrast agent until the patient experiences a sense of fullness and slight discomfort. The urinary catheter is removed if there is no extravasation. During gravity cystography all patients are instructed how to exercise the rhabdosphincter. It is essential that patients can see the elevation of the anastomotic site while contracting the rhabdosphincter, and therefore understand and participate cognitively in these exercises. At 11 days patients are discharged from the hospital.

SURGEON TO SURGEON

Every surgeon has their way of improving the results of radical prostatectomy in terms of continence and potency rates. We consider the use of magnifying loupes and a correctly positioned headlight to be very important, as they aid in identifying the neurovascular bundles and external striated sphincter. By using these two devices a bloodless operating field is more likely. This enables the surgeon to meticulously dissect the prostatic apex and preserve the complex of the rhabdosphincter and the distal part of the neurovascular bundles containing the cavernosal nerves, as well as the branches of the pudendal nerve. The integrity of the rhabdosphincter tendon and pudendal nerve supply is important for preserving continence. Thus, manipulating the urethra should be minimized so that all periurethral tissue distal to the apex remains intact.

Radical retropubic prostatectomy by an experienced surgeon is safe, with fewer complications during and afterward; the duration is usually <2.5 h. With proper patient selection, positive surgical margins are <10%, with pathologically organ-confined prostate cancers in 85–90%. In experienced centres, continence rates reach ≥95% and potency rates ≥80% after surgery.

Correspondence: Wolfgang Horninger, Medical University of Innsbruck, Department of Urology, Innsbruck, Austria. e-mail: wolfgang.horninger@uibk.ac.at
In [1], the following error occurred on page 337.

Figure 3 was reproduced incorrectly. The correct version appears below.

We apologize for this error.

REFERENCES


**FIG. 3.** (a) A schematic of the effect of urgency on the micturition cycle. During an urgency episode, the desire to void increases abruptly, resulting in a void and shortening the intervoid interval, and reducing the volume voided. Therapy can eliminate urgency episodes and thus normalize the intervoid interval. (b) A schematic of two micturition cycles terminated by voids associated with urgency episodes. A refractory period, defined as the interval between voiding and the next urgency episode, can be measured and may be affected by therapy. A warning or deferral time can also be measured as the time from the onset of urgency to voiding.
Abbreviations

Authors may use the abbreviations in this list, without definition when within the main text, but defined when in the Summary. Other abbreviations must be defined on first mention, both in the Summary and in the main text. Abbreviations of units should be those defined by SI.

AIDS acquired immune deficiency syndrome
ANOVA analysis of variance
AUA American Urological Association
BAUS British Association of Urological Surgeons
BCG bacille Calmette-Guérin
BPH benign prostatic hyperplasia
BSA bovine serum albumin
BOO bladder outlet obstruction
CI confidence interval
CNS central nervous system
CT computed tomography
DMSA dimercapto-succinic acid
DRE digital rectal examination
DTPA diethylene-triamine-penta-acetic acid
EDTA ethylenediamine tetra-acetic acid
ELISA enzyme-linked immunosorbent assay
ESWL extracorporeal shock wave lithotripsy
FSH follicle-stimulating hormone
GFR glomerular filtration rate
GnRH gonadotrophin-releasing hormone
GP general practitioner
hCG human chorionic gonadotrophin
HIV human immunodeficiency virus
HPLC high-pressure liquid chromatography
ICS International Continence Society
IGF insulin-like growth factor
IgX immunoglobulin (class X, subclass z)
IPSS International Prostate Symptom Score
IVU intravenous urography
LHRH luteinizing hormone-releasing hormone
LUTS lower urinary tract symptoms
MAG mercapto-acetylglycine
MAG3 mercapto-acetyltriglycine
MHC major histocompatibility complex
MRI magnetic resonance imaging
NHS National Health Service
NSAIDs nonsteroidal anti-inflammatory drugs
PAGE polyacrylamide gel electrophoresis
PBS phosphate buffered saline
PCR polymerase chain reaction
PSA prostate-specific antigen
PTFE polytetrafluoroethylene
PUJ pelvi-ureteric junction
PUV posterior urethral valves
RCC renal cell carcinoma
SD standard deviation
SDS sodium dodecyl sulphate
TCC transitional cell carcinoma
TGF transforming growth factor
TNF tumour necrosis factor
TMN Tumour-Node-Metastasis
TRUS transrectal ultrasonography
TURP transurethral resection of the prostate
UTI urinary tract infection
VUR vesico-ureteric reflux
WHO World Health Organization

Organizer and for further information: Aesculap Akademie GmbH, Am Aesculap Platz, 78532 Tuttlingen, Germany
T +49 7461 95 2001
E info@aesculap-akademie.de
W www.aesculap-akademie.com

American Urological Association Annual Meeting, San Antonio, TX, USA.
T +1 800 908 9414
E convention@auanet.org
W http://www.aua2005.org

XVIII Cuban Congress of Urology and IX Central American and Caribbean Congress of Urology in Centro de Conveniones Plaza America, Varadero, Matanzas, Cuba. President: Dr Alberto Toledo Lozano.
T +53 45 243896
F +53 45 668543
E alberto.toledo@infomed.sld.cu
W www.hospitales.sld.cu


Contact: MECI International Convention Services, Inc., #301 Arin Bldg., 738-2 Yeoksam 1 - dong, Gangnam-gu, Seoul 135-924, Korea
T +82 2 569 5802
F +82 2 569 5803
E ica2005@meci.co.kr

60th Annual Meeting Canadian Urological Association, Ottawa, ON, Canada.
T +1 514 395 0376
F +1 514 875 0205
E central.office@cua.org
W http://www.cua.org
BAUS Annual Meeting Glasgow, UK.
Contact: BAUS, 35-43 Lincoln’s Inn Fields, London WC2A 3PE, UK.
T +1 44 020 7869 6950
F +1 44 020 7404 5048
E admin@baus.org.uk
W http://www.baus.org.uk/

31st Annual Meeting of the International Academy of Sex Research (IASR) Ottawa, Canada.
Contact: IASR, Lucia F. O’Sullivan, PhD, HIV Center for Clinical and Behavioral Studies, New York State Psychiatric Institute, Unit 15, 1051 Riverside Drive, New York, NY 10032-2695, USA
T +1 212 92 86 111
F +1 212 92 86 161
E iasr@northwestern.edu
W http://www.iasr.org

XXV Biannual Congress of the Urological Association of South Africa, Sun City, Pilanesberg, South Africa.
Contact: Toucan Communications
T +1 27 11 886 9895
F +1 27 11 886 9897
W http://www.urosa.co.za

35th Annual Meeting of the International Continence Society, Montreal, Canada.
T +1 847 605 0850
E vicky@icsoffice.org
W http://www.icsoffice.org

4th Biennial World Congress on Men’s Health & Gender (WCMH), Vienna, Austria.
Organization: WCMH Health & Congress management, Lazarettgasse 9/5, 1090 Vienna, Austria
E office@wcmh.info
W http://www.wcmh.info
Congress Office: PROCON Conference, Incentive & Event Management, Odoakergasse 34-36/3, 1160 Vienna, Austria
E office@proconference.at
F +43 1 486 40 40 46
W http://www.proconference.at

10th Biennial Meeting of the Asia Pacific Society for Sexual & Impotence Research (APSSIR) Cairns, Australia.
Contact: Promaco Conventions Pty Ltd., P.O. Box 890, Canning Bridge, Western Australia 6153
T +61 8 93 32 29 00
F +61 8 93 32 29 11
E promaco@promaco.com.au

5th Meeting of the International Society for the Study of Women’s Sexual Health (ISSWSH), Las Vegas, Nevada, USA.
Contact: ISSWSH, 1111 N. Plaza Drive, Suite 550, Schaumburg, IL 60173, USA
T +1847 517 7225
F +1847 517 7229
E isswsh@wjweiser.com
W http://www.isswsh.org

Urology Specialist Registrars’ Spinal Injuries Course. Twice Annually. Sheffield/Wakefield, UK.
Contact: Carole Gregory (secretary to Mr P R Tophill, Consultant Urological Surgeon), Princess Royal Spinal Injuries Unit, Northern General Hospital, Herries Road, Sheffield, S5 7AU, UK
T 0114 271 5645
F 0114 271 5649
E carole.gregory@sth.nhs.uk
W www.aesculap-akademie.com

Organizer and further information: Aesculap Akademie GmbH, Am Aesculap Platz, 78532 Tuttlingen, Germany
T +49 7461 95 2001
E info@aesculap-akademie.de
W www.aesculap-akademie.com