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The new-look and user-friendly website will be a useful addition to what is on offer from the BJU International.

The updated and new look BJU International website was launched on the 15 December 2004. The way it looks reflects the colours and design of the Journal. The address is: http://www.bjui.org. I would encourage you to look at it, as it contains many items of interest. The instructions to authors are all listed, as is information about the journal and its Editors and Editorial Board. You will be able, by using your password, to access current and previous issues of the Journal. It is possible to read a particular article in its entirety, and in many cases, the abstracts of the cited references.

The opportunity also exists to access other websites directly from that of the BJU International by clicking on the appropriate link. I would particularly recommend to you the Urotoday website, which continues to supply valuable information and is kept up to date on a daily basis.

Over the next year, we will be further developing the website. It is intended to make it educational as well as informative, with an additional editorial team looking after it. I feel certain that the changes will be of considerable interest to readers, and that the new-look and user-friendly website will be a useful addition to what is on offer from the BJU International.

The Comment Section of the Journal is widely read and I try to keep the comments at the 'cutting edge'; I am pleased to say that the authors have produced, and continue to do so, very interesting short pieces. This month, Chris Chapple writes about the problem of urgency, both as a comment and also in the Lower Urinary Tract Section of the Journal. I believe that these are important and definitive articles, which will influence our thinking on this subject for some time. I would also like to state once again that the extensive work being put into the Investigative Urology Section is leading to a great increase in the standard of papers being published in this section. It would seem to me that there is now a pleasing balance between molecular biology and urological physiology, with only the very best papers being accepted.

JOHN M. FITZPATRICK
Editor - in - Chief
A conversation between Darracott Vaughan and C. Eugene Carlton Jr

INTRODUCTION

Dr Eugene Carlton has been a leader in urological education. He developed a unique and superb residency program at Baylor. He was instrumental in beginning the Office of Education for the AUA and served as its director and was subsequently president of the American Board of Urology, the AUA and other prestigious organizations.

Dr Carlton was chairman of numerous committees of the AUA, including the Audiovisual, Education Council, Strategic Planning committees. He was also chairman of the Policy committee and the Examinations committee of the American Board of Urology and a Governor of the American College of Surgeons.

He served as President of the following: American Board of Urology, South Central Section of the AUA, the American Urological Association, American Association of Genitourinary Surgeons, and the Clinical Society of Genitourinary Surgeons.

We discuss how he became interested in urology, urological education and what advice he has for the young chairman.

INTERVIEW

Just tell me a bit about growing up and how you got interested in medicine?

I grew up in a small farming community in East Texas, a town of 1200 people. My early role model was my uncle who was a general practitioner. I got interested in medicine early in my life and that was the only thing I ever considered doing.

Where to from high school?

I went to North Texas State University in Denton, Texas for a year and then to the University of Texas, where I graduated in 1951, then Baylor for medical school.

When you got to Baylor, how did you get interested in urology?

I didn't get seriously interested in urology in medical school although one of my subsequent mentors, Dr Abel Leader, who was head of the division of urology as a clinical practitioner, was voted the outstanding teacher for two consecutive years by my class. I was very impressed with him. Coming out of medical school I had several criteria for what I wanted to do. I knew I wanted to do something surgical; I wanted to do something that was not restricted by sex or age group. I wanted a broad range of patients. I wanted something where I could do my own diagnostic work. One of the main things I wanted was a specialty where I could always make a diagnosis and then do something definitive for it.

Military after medical school?

I was married when I got out of medical school and of course had no money. Internships didn't pay anything so I joined the Navy and they paid for my last year of medical school and then gave me an internship at the Naval Hospital in San Diego, an outstanding 2000-bed hospital for active and retired naval personnel and their dependents. That was where I knew I wanted to do urology.

Was there another role model there or did you just decide you liked the field?

I just liked the field and the people that were in urology. I liked the personalities of the urologists. They all seemed to get along together.

How did you decide where to go next?

I was still committed to the Navy for two more years. I applied for a Navy residency and the only one available was at the Naval Hospital in Oakland, California and I wound up doing six months of plastic surgery which I really enjoyed and six months of urology which was not a good learning experience, so I decided to get out of the Navy. I told the chief petty officer there, whose wife was my patient that I wanted out. He was pretty upset with that and said, 'Why don't you stay in the Navy and take a civilian residency?' And I said, 'No, they don't do that for urology, they only do it in neurosurgery.' And he said, 'Well, you never know what those idiots at the Bureau of Medicine and Surgery will do. Let me send in a request.' So he sent a request that I didn't pay a whole lot of attention to, he applied for a residency in urosurgery! And sure enough, they approved it, I called Dr Leader, who was still the chief at Baylor, and he said, 'sure come on, we'll take you.' I started my residency the same day that Russell Scott came there as the first full-time member of the division of urology. So I had the full brunt of Russell from day one and it was just a wonderful experience because he was a hard taskmaster but an outstanding teacher.

Did you have to put more time in the military after that?

I owed them five more years so after my residency was sent to the Naval Hospital on Guam, which was a great experience. After a really tough residency I was housed on the compound of the Naval Hospital, overlooking the Pacific. I had 70 000 people on the island plus the natives on all of the Trust Territory islands as well as the Central Pacific fleet. I had more surgery than I could handle and
lived in an idyllic environment. I saw my kids every day and was home every night. I came back after two years to the naval hospital in San Diego for three years then back to Baylor.

By that time, who was at Baylor?
Russell Scott was head of the division of urology. Brantley Scott, who had been a year behind me in residency, was full-time and there were two other full-time faculty there.

You were a division then. When did it become a department?
I became head of the division in 1971 and got departmental status in 1974.

How did you do that? What’s your advice to young division chiefs?
It depends on the local dynamics. First I went to Mike Debakey and asked him to support departmental status and he of course said no! I gradually went to work influencing members of the executive faculty committee, persuading them one by one. When I had a majority of the executive faculty supporting my application, I went to Mike and told him. He said, ‘I think you should be a department.’

Tell me a little bit about your philosophy of running that department once you became the boss?
I wanted a broadly based model. What I tried to do was to recruit the very best people in the subspecialty areas of urology that I could find and then give them the authority to run their part of the department and then supported them the best I could.

That was a bit of a change because in those days everyone was doing everything so how did you decide that subspecialties were going to be predominant in the future?
I didn’t know that clinical subspecialization was going to develop to the extent that it has. But I thought from research productivity and a teaching standpoint that to develop subspecialty areas in the department was the best way to go.

How did you work with leadership to get the resources for recruitment and sustaining young faculty?
We had pretty much control of our income. All we had to do was give the school a 6% tithe and I set up a practice plan where I got 50% of the money, the practitioner got 50% of the collections, it cost us about 36% in expenses so I used that differential to support new faculty, support research. Russell had gotten started in developing philanthropic support which I continued and we have been extremely fortunate through the years to get good philanthropic support from our community.

How important do you think that is for the departments today?
I think it’s critical. I couldn’t have done what I did and I think Tim Boone, who’s there now, has continued to do that better than either Russell or I did. When Tim took over, we had four endowed chairs; we now have 11 endowed chairs and a commitment for a $20 million institute. I think we would not have been successful had we not been able to go to the community and had they not been as generous as they are to us.

How did you or Tim integrate research into the training program?
Early on we set up a one-year research activity. All residents are required to do one year of research.

That’s still going on? And how do you fund that?
Yes. I funded it out of philanthropic dollars, practice income. I’m not really sure how Tim is doing it now. One thing that we have now that I’m really happy about is an endowed chair for education. One of our faculty, Mike Coburn, has been certified as Master Teacher and occupies the chair in education that gives him the income to do innovative things.

I think we have under-rewarded teaching. Where did the Master Teacher concept come from?
Baylor developed a Master Teacher Program to train selected faculty to be outstanding teachers. Mike was the first faculty person at Baylor to complete this program.

During the years there as chairman, what are you most proud of accomplishing?
First of all, the success of the subspecialty program. We have really good people in all of the subspecialty areas; then I guess the educational program. We developed a really good resident education program that we are committed to.

Talking about education, you were involved right from the beginning of education at the American Urological Association. Tell me a little bit about how that got started?
One of your colleagues from New York, John Lattimer, who was president of the AUA, heard about our residency education program. He was going to be in town to give a talk and asked if he could look over our educational program. I didn’t have any idea why and then I got a call a little while after that asking me if I would set up a continuing education program for the AUA. I went around to the various specialty societies, saw what they were doing, which was not much, and then set out to design a continuing medical education program, a critical component of which was to have a full-time director of education. I submitted that back to John Lattimer and the Executive Committee of the AUA approved it, they then asked me to search for a director. At that time Russell Scott was in Saudi Arabia running the King Faisal Hospital and desperately trying to find a way to get out of his contract over there. We found him vacationing on the island of Cyprus and asked him if he would like to be the director. He came back from Saudi and set up the Office of Education in Aspen.

I think it is the best Office of Education of any subspecialty, would you agree?
It certainly was for a long time and as far as I know still is. Russell had it for four years and then I ran it for 17 or 18 years, then Joe Corriere and now Dave McCullough.

Where are we going with resident education as you look forward?
I think the first thing we are going to have to do is decide what we are going to do about this tiered system of urological practice because that is going to affect our programs. I think that’s the first issue that has to be resolved and then we are going to have to design training programs to fit those tiers if that’s the way we go.

What do you think the major challenges are for the AUA these days?
I would hope that they would increase their focus on education and research. There are the two areas where they can be of the most service to their members. To me, education is the prime mission of the AUA and so that’s got to be a primary focus.

You’ve retired. What do you do?
I help Tim Boone with a couple of administrative things. I help him with fund raising but I don’t do much of anything else anymore. When I retired I took over a foundation for retarded children that was in trouble. Over the last ten years we’ve got that up and running and very successful now and I am pulling out of that. So I’m raising grandchildren, trying to play golf, fishing. Ann and I do a lot of fishing and travel.

You had a smooth transition. What advice do you have for transitions in departments?
I’m a very strong believer in succession planning. I think you need to have a very strong plan so that you control the succession and then, once you have your successor in place, I think you need to get out of the way and support that successor and not interfere with what he or she is trying to do.
INTRODUCTION

As the most frequently diagnosed male malignancy, second only to lung cancer as a cause of cancer mortality, prostate cancer represents a major health problem in the USA. In the past decade there has been an increase in the detection rate of prostate cancer and a significant increase in the proportion of men with early confined disease. This trend toward early detection has resulted in a proportionally significant increase in the diagnosis of prostate cancer in many men with clinically insignificant disease, based on cancer volume (<1 mL) and slower growth rate [1]. According to one report, 30–40% of men aged >50 years have prostate cancer, but only 8% of cancers become clinically significant [2]. The current emphasis on curative treatment includes early detection and radical primary local treatment of the prostate and adjacent tissue with surgery or radiation. However, it is well recognized that such radical treatment is associated with significant morbidity and can be ‘over-treatment’, greatly affecting the quality of life in a subset of patients with localized disease. Patients frequently ask why the urologist cannot treat just the diseased part of their prostate. Few other malignancies share such a dilemma. The management of breast cancer has developed from radical treatment, with extensive disfiguring dissection of the anterior thoracic wall, to localized treatment with wide excision or ‘lumpectomy’ with or without axillary clearance.

DETERMINING THE LOCATION OF CANCER

The prostate is arbitrarily divided into anatomical zones describing the ductal drainage systems. The posterior peripheral zone comprises 70% of the prostate volume and is the location of 60–70% of prostate cancers. Another 10–20% of prostate cancers are in the transition zone. The central zone, which accounts for 25% of prostate volume, is the site of 5–10% of prostate cancers. Prostate cancer is a multifocal disease that involves both lobes of the prostate in two-thirds of cases [3]. The rate of cancer detection is higher in saturation-biopsy series than with the standard extended-core biopsy practised in most urological clinics. Furthermore, the recent development of three-dimensional (3-D) computer modelling of the prostate both provides biopsy sampling accuracy and assists in localizing significant cancer foci [4].

Clearly, a vital requisite for the successful focal treatment of a confined prostate cancer involves the development of intraprostatic imaging models with high sensitivity for detecting significant cancer foci. Promising steps toward that end include new advances in endorectal MRI coupled with MR spectroscopic imaging (MRSI), radioisotope tracer techniques, dual imaging with CT and ProstaScint® monoclonal antibody scanning, among others.

CURRENT STATUS AND FUTURE TRENDS

Attempts to treat one side of the prostate with target cryotherapy are currently underway. Although promising, such an approach appears to limit treatment to a few patients with unilateral disease. In addition, this technique requires the exclusion of cancer on the contralateral side. Studies have shown that sextant TRUS-guided biopsies cannot predict unilateral disease, and it is vital that a TRUS saturation biopsy be used to achieve an accurate diagnosis. At our institution we are in the process of conducting a phase II trial to study the feasibility of focal target ablation of prostatic foci based on a saturation biopsy, using patented 17 G cryoneedles. A computerized 3-D real-time topographical reconstruction of the prostate has been developed to aid in identifying clinically significant cancers (>1 mL) islands using zonal mapping of the prostate. Although the development of this model is still in its early stages, it will aid in the focal ablation of prostate cancer with minimally invasive techniques, thereby achieving curative treatment in men with localized disease.

FOCAL THERAPY IN PROSTATE CANCER: FUTURE TRENDS

AL BARQAWI and E. DAVID CRAWFORD – University of Colorado Health Sciences Center, Denver, Colorado, USA

POTENTIAL ADVANTAGES AND DISADVANTAGES OF THE FOCAL TARGET THERAPY APPROACH

Potential advantages of focal therapy in treating localized prostate cancer include maintaining curative and survival rates comparable with those of conventional primary surgical and radiation therapy, with no increase in complications, e.g. erectile dysfunction, urinary incontinence and rectal injury. This approach is cost-effective, based on a shorter time required for the procedure and a briefer inpatient hospital stay. In addition, focal therapy will improve patient satisfaction and quality of life.

Potential drawbacks to this approach include the risk of incomplete treatment, which may be a result of missed cancer foci and inadequate ablation to the target tissue. However, these possible disadvantages can be overcome with current technical advances in target-ablation probes using cryoneedles, high-frequency ultrasound, thermal and laser machines to achieve confined and complete target destruction. The National Cancer Institute is currently recruiting patients for
the presence of infection or other obvious pathology, the ICS standardization committee suggested synonymous terms to be the ‘urgency/frequency syndrome’ or ‘urge syndrome’ [1]. Therein lies a problem, as whilst the terms ‘urgency’ and ‘urge’ can be suggested to be subtly different, with urge as a normal sensation and urgency an abnormal sensation, i.e. as defined by the ICS as ‘the complaint of a sudden compelling desire to pass urine which is difficult to defer’. This implies that there is a continuum between the normal desire to void and urgency, a hypothesis for which there is no evidence at present. A strong case can be made for suggesting that the definition of urgency should be further qualified by adding the phrase ‘for fear of leakage’, which was previously in the definition but abandoned at the time of the last revision of terminology. It is clear that from discussions with European and Asian colleagues that the nuance of the difference between urgency and urge does not translate into other languages, and indeed a cursory review of the current situation clearly emphasizes the problem even in English. Whilst in the standardization report both the term ‘urge syndrome’ is clearly suggested to be synonymous with the urgency/frequency syndrome, and incontinence associated with OAB is identified as ‘urge incontinence’, such descriptions should, according to the ICS standardization committee’s own description, be the urgency syndrome and urgency incontinence. This confusion in terminology in current publications is also clear from a review by Chapple et al. published in this issue [2].

TERMINOLOGY

How can we communicate this term to colleagues and assess the outcome of therapy in patients? It is clear from the present discussion that the terms ‘urge’ and ‘urge incontinence’ should be abandoned, in favour of the terms ‘urgency’ and ‘urgency incontinence’, and a strong case can be made for suggesting that the definition of urgency should be further qualified by adding the phrase ‘for fear of leakage’. Cardozo et al. [3] address the important issue of measuring urgency in their interesting paper in the next issue of BJU International, where they carried out a detailed psychometric evaluation of their Urgency Perception Scale (UPS). They state that ‘physician reviewers’ felt that the conceptualization of the UPS was ‘valid and rational’, but acknowledge in the discussion that ‘the UPS is not a diagnostic tool and cannot distinguish ‘urge’ incontinence from stress incontinence’. They correlated the UPS in detail against voiding diaries and state-of-the-art patient assessments, including the generic Medical Outcomes Study Short-Form Questionnaire on incontinence.

It is important to acknowledge that this approach is not universally applicable to all patients, e.g. those who have perineal and extracapsular extension of the tumour may not benefit from focal treatment. Other circumstances that limit the usefulness of focal therapy include: (i) the inability to use current postoperative guidelines for PSA to monitor efficacy and recurrence, as prostatic tissue will remain; and (ii) the inability to have a final pathological report depicting the Gleason score and the extent of extracapsular invasion (margin status), which may delay further treatment for these patients.

CONCLUSIONS

The use of focal target therapy for prostate cancer based on a real-time 3-D model of the prostate may potentially achieve complete destruction of all significant cancer foci within the prostate in an effective and cost-effective manner. The recent emergence of high-resolution imaging tools coupled with advances in computerized modelling software should be used in the near future to give alternative treatment options to men with localized, early-stage cancer. This approach is an important step in our quest for better ways to treat the disease while maintaining a good quality of life for our patients.

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THE URGENCY OF THE PROBLEM AND THE PROBLEM OF URGENCY IN THE OVERACTIVE BLADDER

INTRODUCTION

The importance and relevance of urgency as the cardinal syndrome of the overactive bladder syndrome (OAB) has been clearly recognized by the ICS. Urgency is now considered by many to be the pivotal clinical symptom in OAB, as it is the symptom which leads to frequency, nocturia and incontinence; furthermore, it is a surrogate endpoint for patients having better control, as shown by what patients say when they report a successful outcome on therapy. Nevertheless, the problems associated with the use of the term urgency are many and include terminology and the definition of urgency, the communication of this concept to both clinicians and patients alike, and ultimately the measurement of urgency, which is the subject of a review and a paper in this issue of the BJU International.

In addition to the term OAB, which is defined as ‘urgency with or without incontinence, usually with frequency and nocturia’ in the absence of infection or other obvious pathology, the ICS standardization committee suggested synonymous terms to be the ‘urgency/frequency syndrome’ or ‘urge syndrome’ [1]. Therein lies a problem, as whilst the terms ‘urgency’ and ‘urge’ can be suggested to be subtly different, with urge as...
Cardozo et al. [3] by stating that 'The UPS was found to be conceptually valid but to have uncertain responsiveness based on the few response options available to the patients.' In particular, a patient who says that he/she is usually able to finish a task before going to the toilet is given no room to improve despite still having OAB. The UPS also lacks temporal characteristics that would enhance its ability to be understood by patients. For example, 'I am not able to hold urine' is not a clear statement in the absence of a specified period. Not being able to hold urine for 30 min is certainly different from not being able to hold urine for 3 h. The UPS, quite correctly, purports to measure the perception of urgency rather than urgency per se. However, it has at least one category (response #3) that appears to be inconsistent with the compelling nature of urgency as defined by the ICS [1]. Similarly, response #1 (‘I am usually not able to hold urine’) would appear to be applicable to urgency with incontinence only. In this context it is important to consider that only a third of patients with OAB have urgency incontinence.

Clearly urgency is a symptom and as such is difficult to define, to communicate to both patients and colleagues alike, and to measure and quantify, notwithstanding the additional variable introduced by inter-individual variation. Aspects such as how the symptom of urgency differs from ‘urge’ or ‘the normal desire to void’ (the latter in our view being a preferable term), remain unresolved. Once these terminological issues have been resolved then it will be possible to investigate the other important characteristics of the symptom of urgency. For instance, where the sensation is located; in the suprapubic area or the perineum?; are there in fact differences in shorter ‘warning or postponement time’ in women rather than men; is there a difference in the sensation of urgency in people with a neurological cause rather than those with idiopathic detrusor overactivity?

It is evident that we are now reaching a clearer understanding of ‘both the problem of urgency and the urgency of the problem’, and agreeing on standardized unambiguous terms and clear definitions are essential steps if we are to advance our knowledge in this field.

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IS PELVIC LYMPHADENECTOMY REALLY NECESSARY IN PATIENTS WITH A SERUM PROSTATE-SPECIFIC ANTIGEN LEVEL OF <10 ng/mL UNDERGOING RADICAL PROSTATECTOMY FOR PROSTATE CANCER? FIONA C. BURKHARD, MARTIN SCHUMACHER, GEORGE N. THALMANN and URS E. STUDER – Department of Urology, University of Bern, Bern, Switzerland

INTRODUCTION
The necessity and extent of pelvic lymph node dissection (LND), particularly in patients with a PSA level of <10 ng/mL remains a subject of intense debate. Overall, in our series of 463 patients with localized prostate cancer and without previous therapy (radio- or hormonal
therapy), who all had an extended LND, lymph-node metastasis was detected in 24% [1]. Extended lymphadenectomy in this series included the nodes along the external iliac vein, the obturator fossa and along the internal iliac artery, and a median (range) of 21 (6–75) nodes were removed per patient. Stone et al. [2] compared 150 patients with modified and 39 with extended LND; not only did they find, as was to be expected, a significant difference in the number of nodes removed, 9.3 vs 17.8 (P < 0.05), but also three times as many patients with lymph-node metastasis, 7.3% vs 23.1% (P = 0.02). This was confirmed by Heidenreich et al. [3] in a study comparing a historical control group with standard (external iliac vein and obturator fossa) and a contemporary group with extended lymphadenectomy (external iliac vein, obturator fossa, internal iliac artery, common iliac vessels and presacral). A median of 11 (6–19) and 28 (21–46) nodes were removed for standard and extended LND, respectively. At the same time the number of patients with lymph-node metastasis increased from 12/100 to 27/103. Heidenreich et al. further concluded, that as of all nodes removed only three were found to be positive along the common iliac vessels and in the presacral area, removing lymphatic tissue from these regions could be neglected.

In contrast, the importance of removing the nodes along the internal iliac artery is becoming increasingly clear. In our series 17% of patients had positive nodes exclusively in this area, and in [4] and [5], 29% and 19%, respectively. The proportion of patients with nodes either exclusively in this area or in combination with another location was 59% in our and 67% in the series by Tenaglia and Iannucci [5]. Without removing the tissue along the internal iliac artery a significant number of patients would be left with diseased nodes.

It is often stated that once patients have node-positive disease this should be considered systemic and treated accordingly, and that removing further nodes shows no benefit. However, in our series the number of positive nodes removed correlated inversely with the chance of remaining biochemically disease-free. The rate of biochemical progression, symptomatic tumour progression and death was significantly lower in patients with only one lymph node involved, so that there may be a potential cure for patients with low metastatic load if all diseased nodes are removed. In accordance, Stein and Skinner (unpublished data, courtesy of Stein and Skinner, University of Southern California, December 2003) reported an ~40% chance of PSA recurrence-free survival after 10 years in patients with stage D1 prostate cancer, again implying a potential chance of cure even in these patients.

In contrast, Dimarco et al. [6] detected no survival advantage after extended lymphadenectomy for prostate cancer. In that study the median number of nodes removed decreased from 14 between 1987 and 1989, to five between 1999 and 2000. Interestingly, removing more nodes in the earlier period led to similar results for disease progression and survival as removing fewer nodes in the later period. As T-stage migration over time is an accepted phenomenon this may imply that, thanks to a more extended lymphadenectomy, patients with higher-stage disease had comparable survival chances to a recent population with earlier stage disease.

The need for extended lymphadenectomy is further enhanced by the analysis of Di Blasio et al. [7] showing that the number of nodes removed is associated with progression (P = 0.044). Removing ≥13 nodes had the lowest risk of disease progression, regardless of nodal disease status. Bader et al. [8] reported similar findings, with 16%, 12%, 8% and 8% of patients showing disease progression after removing 0–4, 5–9, 10–14 and >14 nodes for pT1/pT2N0 prostate cancer, respectively.

Our reported series has been criticised for not representing the actual current situation; the series included many patients with locally advanced disease and a high median PSA level of 11.4 ng/mL. This may not reflect the current situation, where mainly patients with a PSA of <10 ng/mL are treated. Thus we discriminated between patients with a PSA of <10 and ≥10 ng/mL. Not unexpectedly, the incidence of positive nodes increased to 33% for the patients with a PSA of >10 g/mL (Table 1). What was more surprising was that 11% of patients in the low-PSA group had positive nodes. The distribution of the positive nodes was similar in both groups, with ~20% found exclusively along the internal iliac artery (Table 1). Another interesting finding was that in patients with positive nodes, despite a PSA level of <10 ng/mL, two-thirds had organ-confined disease. Thus, neither PSA or local T-stage appear to be valid factors to determine the need for LND. When assessing the Gleason score we found that, as expected, with increasing pathological Gleason score more patients had metastatic disease. Only 3% with a Gleason score of ≤6, vs 17% with a score of ≥8 (Table 2). Can we therefore restrict LND to patients with a Gleason score ≥6 and a PSA level of <10 ng/mL in the prostate biopsies? Probably not; as ~30% of biopsies are understaged.

Many surgeons tend to base their decision on nomograms based on limited or standard LND; these nomograms should help to determine the stage of disease based on clinical staging, the serum PSA value and the preoperative Gleason score. Table 3 shows the predicted values (Partin nomogram) and the results of the Heidenreich et al. [4] and our series, where all patients underwent extended LND. Both groups find a much higher
A positive effect on survival was reported as a result of extended lymphadenectomy (Table 5) [9–12]. Why should prostate cancer be an exception?

In summary, an extended lymphadenectomy should be used in all patients having LND and radical prostatectomy for prostate cancer, even those with a PSA level of <10 ng/mL. Special attention should be placed on removing the lymphatic tissue along the internal iliac artery, as a significant number of positive nodes are found in this area, which is often neglected. Because of the higher probability of detecting positive nodes during lymphadenectomy, nomograms based on standard LND should be applied with caution. The impact of extended lymphadenectomy on disease progression and survival remains to be confirmed. However, there are certain indications, that as in other forms of cancer, removing all diseased nodes may have a positive effect on the course of the disease.

REFERENCES


TABLE 2 The Gleason score of the prostatectomy specimen in patients with positive lymph nodes and a serum PSA of <10 ng/mL.

<table>
<thead>
<tr>
<th>Gleason score</th>
<th>No. patients with +ve nodes/ N patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>0/12</td>
</tr>
<tr>
<td>3</td>
<td>0/11</td>
</tr>
<tr>
<td>4</td>
<td>1/39 (2)</td>
</tr>
<tr>
<td>5</td>
<td>3/62 (5)</td>
</tr>
<tr>
<td>6</td>
<td>6/75 (8)</td>
</tr>
<tr>
<td>7</td>
<td>6/52 (12)</td>
</tr>
<tr>
<td>8</td>
<td>9/14 (38)</td>
</tr>
<tr>
<td>9</td>
<td>6/12 (50)</td>
</tr>
<tr>
<td>Totals</td>
<td>31/287 (11)</td>
</tr>
</tbody>
</table>

TABLE 3 The predicted incidence of lymph node metastasis according to the Partin Tables, and the incidence in patients with extended lymphadenectomy.

<table>
<thead>
<tr>
<th>Partin</th>
<th>[3,4]</th>
<th>[1]</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>321</td>
<td>596</td>
</tr>
<tr>
<td>PSA &lt; 10 ng/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2–4</td>
<td>0</td>
<td>1.4</td>
</tr>
<tr>
<td>5–7</td>
<td>2–8</td>
<td>10</td>
</tr>
<tr>
<td>8–10</td>
<td>8</td>
<td>57</td>
</tr>
<tr>
<td>PSA 10–20 ng/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2–4</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>5–7</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>8–10</td>
<td>27</td>
<td>57</td>
</tr>
</tbody>
</table>

incidence of nodal disease than predicted; this should be considered when relying on such tables.

The impact on disease progression and survival remains unconfirmed because of the relatively benign course of disease in prostate cancer, necessitating a follow-up of 10–15 years. However, there are findings indicating an improved course of disease after extended LND with removal of all diseased nodes, especially in patients with low-volume metastatic disease. Of patients with only one positive node, 75% remained free of tumour progression and only 14% have so far died from prostate cancer in the series by Bader et al. [8] (Table 4). In other forms of cancer, e.g. stomach, oesophagus, pancreas and lung, a positive effect on survival was reported as a result of extended lymphadenectomy (Table 5) [9–12]. Why should prostate cancer be an exception?

In summary, an extended lymphadenectomy should be used in all patients having LND and radical prostatectomy for prostate cancer, even those with a PSA level of <10 ng/mL. Special attention should be placed on removing the lymphatic tissue along the internal iliac artery, as a significant number of positive nodes are found in this area, which is often neglected. Because of the higher probability of detecting positive nodes during lymphadenectomy, nomograms based on standard LND should be applied with caution. The impact of extended lymphadenectomy on disease progression and survival remains to be confirmed. However, there are certain indications, that as in other forms of cancer, removing all diseased nodes may have a positive effect on the course of the disease.
COMMENTS


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Abbreviations: LND, lymph node dissection.

CARDIAC FAILURE AND BENIGN PROSTATIC HYPERPLASIA: MANAGEMENT OF COMMON COMORBIDITIES MAJID SHABBIR, JAYMIN S. SHAH* and ROGER S. KIRBY – The London Clinic, Harley Street and *The Heart Hospital, London, UK

INTRODUCTION

An increase in the ageing population coupled with improved outcomes from cardiac disease has led to a higher prevalence of heart failure. There are 900 000 people with heart failure in the UK, with a mean age of 76 years, and the size of this population is steadily increasing [1]. The prognosis of heart failure can be worse than many malignancies, with a mortality of 40% in the first year amongst newly diagnosed patients, decreasing to 10% per year thereafter [2]. Patients with cardiac failure have numerous comorbidities and thus take many drugs; these factors affect the patients’ quality of life.

In urology, the increase in the number of elderly men has led to more patients presenting with troublesome LUTS secondary to BPH. Many of these patients will have heart failure and their optimum treatment requires a holistic approach, aiming to improve urinary symptoms without worsening their coexistent cardiac condition, and vice versa. An accurate clinical assessment and an appreciation of the effects of drug therapies used in treating both conditions is necessary to better manage such patients.

CARDIAC FAILURE

Cardiac failure occurs when the heart fails to pump blood at a rate sufficient for metabolic requirements; it develops because of an imbalance in one of four components of cardiac function: (i) myocardial contractility; (ii) ventricular pre-load; (iii) ventricular after-load; and (iv) heart rate.

While the normal heart can tolerate wide variations in these factors, the diseased myocardium has a limited reserve. In the western world, coronary artery disease accounts for most cases of heart failure. Other causes include hypertension, alcohol, viral infections, idiopathic, infiltrative conditions and drug toxicity.

Heart failure usually presents with breathlessness, fatigue, exercise intolerance and fluid retention. Other nonspecific symptoms include anorexia, abdominal bloating and nocturia, with the latter often mimicking the presentation of troublesome LUTS from urological pathology. Clinical examination may reveal signs of left (central) or right (peripheral) ventricular failure, or a combination of the two.

Heart failure symptoms can be assessed functionally using the New York Heart Association (NYHA) classification (Table 1). The NYHA functional class tends to deteriorate unevenly over time and the severity of symptoms does not necessarily equate with the severity of the underlying heart problem [3]. Consequently this system alone is too insensitive to predict outcome or assess response to treatment.

An accurate assessment of cardiac function is important in managing patients with heart failure. A recent study highlights how urologists often underestimate the importance of comorbid risks and overemphasize the importance of age when selecting patients suitable for operative management [4]. There is therefore now an increasing trend towards an assessment for surgery based on overall performance status rather than age alone.

The investigation of patients with known heart failure should include blood tests to exclude concurrent anaemia, electrolyte disturbances and renal impairment secondary to medications. Electrocardiograms may elucidate an underlying cause and a chest X-ray may show signs of cardiomegaly and pulmonary venous congestion.

A key investigation in patients with heart failure is the assessment of left ventricular function using transthoracic echocardiography. This can assess atrial and ventricular size and function, and can also detect underlying valvular or myocardial

<table>
<thead>
<tr>
<th>Class</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>No limitations: Ordinary physical activity does not cause fatigue, breathlessness or palpitation. (Asymptomatic left ventricular dysfunction is included in this category).</td>
</tr>
<tr>
<td>II</td>
<td>Slight limitation of physical activity: Such patients are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, breathlessness or angina pectoris (symptomatically ‘mild’ heart failure).</td>
</tr>
<tr>
<td>III</td>
<td>Marked limitation of physical activity: Although patients are comfortable at rest, less than ordinary physical activity will lead to symptoms (symptomatically ‘moderate’ heart failure).</td>
</tr>
<tr>
<td>IV</td>
<td>Inability to carry out any physical activity without discomfort: Symptoms of congestive cardiac failure present even at rest. With any physical activity there is increased discomfort (symptomatically ‘severe’ heart failure).</td>
</tr>
</tbody>
</table>

TABLE 1 The NYHA classification
abnormalities. It can measure ventricular ejection fraction noninvasively, with values of <40% indicating significant left ventricular dysfunction. This is an important factor in assessing outcome and response to therapy. Additionally this test can give vital information to help grade the suitability for general anaesthesia (American Society of Anesthesiology grade).

TREATMENT

Many of the pharmacological therapies used for treating heart failure have important implications to the urological patient. Figure 1 shows the UK treatment algorithm for heart failure.

An understanding of the complications of the various drug therapies is paramount in managing concurrent heart failure and BPH. Treatment with diuretics accentuates the symptoms of BOD and, by ironically worsening symptoms scores (IPSS) makes patients more likely to present to their urologist with troublesome LUTS. Diuretics worsen urinary urgency, and severe symptoms can lead to poor patient compliance with treatment and a reduction in their quality of life.

Common side-effects of treatment with angiotension-converting enzyme (ACE) inhibitors, diuretics and angiotension-II receptor antagonists include postural hypotension and impairment of renal function. Postural hypotension is also seen with β-blockers, and this iatrogenic decline in blood pressure can compound the hypotension commonly seen with α-blockade in treating BPH. Concurrent treatment with all these drugs should therefore be closely monitored.

Another important consideration is the supposed increased susceptibility to heart failure reported with α-blockers such as doxazosin. The recent Anti-hypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) study was a randomized, double-blind trial investigating the effect of antihypertensive therapy with doxazosin (1–8 mg) vs the diuretic chlorthalidone (12.5–25 mg), the calcium-channel blocker amlodipine (2.5–10 mg), and the ACE inhibitor lisinopril (10–40 mg). The main outcome of the trial was the effect of treatment on the incidence of fatal and nonfatal cardiovascular events in a group of patients aged >55 years with ‘high-risk’ hypertension, defined as patients with hypertension and one or more coronary heart disease risk factors [5].

While doxazosin gave similar results to chlorthalidone for the primary endpoint of fatal coronary heart disease and nonfatal myocardial infarction, patients taking doxazosin had twice the risk of developing heart failure. As a consequence the doxazosin arm of the study was terminated early. These results have sparked much debate and criticism worldwide [6], and at present the exact role of α-blockers in managing hypertension remains unclear. However, it is important that urologists are aware of the potential risks involved in doxazosin use, especially as it is often used specifically in patients with concurrent hypertension and BPH. At present it is remains uncertain whether doxazosin should be avoided in patients with established heart failure. It is possible that the use of the more uroselective α-blockers such as tamsulosin may provide a way around these potential problems, although at present there is no evidence to confirm this theory.

Another consideration in managing heart failure is the potential effect of this condition, and its treatment, on sexual function. Patients with heart failure often have impaired sexual function caused by a variety of factors, including fatigue, fear of having sex after a myocardial infarction, reduced exercise tolerance and orthopnoea. In addition,
treatment with diuretics and β-blockers can also cause erectile dysfunction. Ejaculatory problems, impaired orgasm and a decreased libido are also commonly reported by patients taking cardiovascular medication. BPH itself can also result in erectile dysfunction, and a clear medical and drug history in patients with both conditions will ascertain how much the presence of cardiovascular factors contribute to each case. Alterations to drug regimens and psychotherapy may improve sexual function in patients with heart failure, and the treatment of such patients is best approached in conjunction with a cardiologist. Heart failure itself is not an absolute contraindication to the use of oral phosphodiesterase type 5 inhibitors, e.g. sildenafil, although it is important to assess the patient’s cardiovascular risk and functional status, in addition to excluding the concurrent use of oral nitrates. A recent prospective, placebo-controlled, double-blind crossover trial showed sildenafil to be both safe and effective for treating erectile dysfunction in patients with NYHA class II and III heart failure, causing no significant adverse effects [7].

In summary, the changing trend in population dynamics has increased the prevalence of elderly men seeking treatment for symptomatic BPH. This is often accompanied by comorbidity and polypharmacy. The modern urologist must therefore be aware of the effect of BPH treatments on their patients’ overall well-being. With the incidence of heart failure set to continue to rise, it is vital that the urologist is familiar with the important issues involved in the successful simultaneous management of both these common conditions.

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Mini-reviews

This month there are two mini-reviews on aspects of prostate cancer. The first, from the USA, presents the implications of surgical margin status after radical prostatectomy and the potential role of adjuvant radiation therapy. The second, from the USA and Belgium, discusses the use of hormonal therapy for PSA-only recurrence of prostate cancer after previous local therapy.

In the third mini-review, the condition known as hypoactive sexual desire disorder is described, and that it is often ignored or erroneously treated as erectile dysfunction suggests to the authors that education of doctors and patients is required. Finally, there is a mini-review of conventional and alternative methods for providing analgesia in renal colic.

Surgical margin status after radical retropubic prostatectomy

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KEYWORDS
prostate adenocarcinoma, radical prostatectomy, surgical margin, prognosis

INTRODUCTION
Since the early 1980s, improved knowledge of male pelvic anatomy, along with the refinement of surgical technique, have led to a dramatic change in the management of localized prostate cancer. There has been a dramatic increase in the number of radical prostatectomies (RPs) in the USA over the past 20 years (peaking at 104 000 in 1992–93) [1]. In addition, the incidence of lymph node and/or seminal vesicle involvement has decreased considerably over the past few years [2,3]. As a result, interest has recently focused on the relationship between surgical margin status and disease progression after RP. In this mini-review we discuss the implications of surgical margin status after RP and the potential role of adjuvant radiation therapy.

DEFINITION OF SURGICAL MARGIN STATUS
Current reports give several definitions of a positive surgical margin after RP; notably, Zeitman et al. [4] assign a positive margin status if tumour is present at or within 1 mm of the surgical margin. However, Epstein et al. [5,6] found that if the tumour is not actually cut across and/or at the inked surface (the external surface of the prostate is covered with India ink before sectioning), a ‘close surgical margin’ (<0.1 mm) should not be designated as a positive surgical margin. The authors state that ‘close margins’ are unrelated to the tumour that would have been left within the patient, nor do they indicate any greater risk of disease progression after RP. Therefore, a positive surgical margin is generally defined as extension of tumour to the inked surface of the resected specimen.

CAUSE AND SITE OF POSITIVE MARGINS
Accidental incision into the prostate and a site of tumour that may not extend beyond the prostate often result in positive surgical margins. This ‘capsular incision’ most frequently occurs in the apex and may account for >70% of cases with a positive surgical margin [7]. Accordingly, Stamey et al. [8] and Ackerman et al. [9] found that capsular incision represented 45% and 87% of positive apical margins, respectively, seemingly resulting from an artefact of sectioning the apex [10]. Another important factor is the ‘detrusor apron’, a continuation of the anterior bladder wall with the pubis, which constitutes a large portion of the anterior fibromuscular stroma [11]. This stroma covers the entire anterior and anterolateral surface of the glandular prostate, hence transection can typically produce a capsular incision and lead to a potential ‘false-positive’ margin [11].
Positive margins resulting from capsular incision are also typically found in the posterior margin and the mid portion of the gland [8,9]. Encouragingly, a higher risk of progression after RP is not usually linked with positive surgical margins arising from capsular incisions [7,12–14].

Failure to adequately address extraprostatic extension of tumour, which most often occurs posterolaterally in the region of the neurovascular bundles (NVBs), may lead to a positive margin. NVBs are often spared despite bulky disease, in an attempt to safeguard potency. The value of this practice has been questioned, as recent evidence indicates that margin status is not significantly different between nerve-sparing and non-nerve-sparing surgery (retropubic or perineal) when patients are matched for stage and grade [7]. However, it is notable that attempts to preserve adjacent vital structures such as the rectum, rather than NVBs, more commonly result in an extraprostatic extension [7].

INCIDENCE OF POSITIVE SURGICAL MARGINS

Epstein et al. [7,13] examined RPs undertaken by one surgeon at the Johns Hopkins Hospital, and found that over time there was a striking change in the incidence of positive margins. Reviews from 1982 to 1988 showed that 41% of RP specimens had positive margins, decreasing to 16% between 1994 and 1995 [7,13]; when only stage T1c disease was considered, this rate decreased further to 8%. In 1999, the incidence of positive margins for all patients operated by the same surgeon was 5.8% [7]. Other institutions have also reported a decline in positive surgical margins, including more organ-confined disease and lower positive surgical margins [18–20]. During the past decade, patient selection has also been important. Men with high biopsy Gleason scores (≥7) and/or elevated serum PSA levels (>10 ng/mL) are less likely to have organ-confined disease, and hence are less likely to be recommended to undergo surgery [21,22].

To improve continence rates, interest has been generated in bladder-neck preserving prostatectomy, but there is concern that this might be associated with more positive surgical margins. Unfortunately, although recent studies indicate that for selected patients (i.e. T1c–T2a, low-volume and –grade disease) preserving the bladder neck does not result in more positive surgical margins or disease progression, continence rates have not greatly improved either [23–24].

MARGIN STATUS AND DISEASE PROGRESSION

The likelihood of progression is considered to be significantly greater for men with true positive surgical margins than men with negative margins [25]. Two studies predicted the progression-free probability at 5 years after RP to be 81–83% for margin-negative disease, decreasing to 58–64% for margin-positive disease [15,17]. Multifocal and extensive positive margins are regarded as higher risks for progression than solitary and focally-positive margins [7]. Similarly, margins positive at the bladder base indicate a higher risk of biochemical failure [26].

In keeping with other reports, Fig. 1A (data from our institution) shows that a positive margin status confers higher biochemical disease recurrence. Despite the importance of margin status in predicting progression, it would be a mistake to ignore the impact of other variables, including seminal vesicle and lymph-node status, extraprostatic extension, and prostatectomy Gleason score, all of which affect the prognosis adversely.

The Gleason score is the most powerful predictor of progression after RP [7]. Fig. 1B shows the influence of Gleason score on biochemical recurrence-free survival estimates after RP. Biochemical recurrence rates for positive margins with a Gleason score of 2–6 are similar to those for negative margins with a Gleason score of 7–10. However, when seminal vesicles and lymph nodes are negative and the Gleason score is 7–10, a positive surgical margin predicts a high rate of failure.

ADJUVANT RADIATION THERAPY FOR POSITIVE MARGINS

There is no current consensus on the need for or the best treatment for positive surgical margins. Nevertheless, intuitively, men with positive margins are likely to fail locally, and so are suitable candidates for adjuvant external beam radiotherapy (EBRT). Recently, Leibovich et al. [27] studied 76 men with organ-confined disease (T2N0) and a single
positive margin, who received early EBRT (within 3 months of surgery), and matched them 1:1 with controls who did not receive adjuvant EBRT; the estimated 5-year clinical and biochemical progression-free survival was higher in the early EBRT group. Notably, although similar results were reported by others [28,29], no studies have yet shown an overall survival benefit. Many margin-positive tumours reflect high-grade and/or -stage disease with occult distant metastases, despite presenting with presumed clinically localized disease. Thus although a positive margin may indicate local disease recurrence, unfortunately it does not exclude occult distant disease. Han et al. [30] recently determined whether biochemical failure after RP in men with Gleason score ≥7 disease and positive surgical margins is associated with distant metastasis or local tumour recurrence. Isolated clinical local recurrence was rare amongst these men; hence EBRT given when PSA levels increased controlled the disease poorly. Accordingly, men with a Gleason score of ≥7 and positive surgical margins should be considered for a systemic approach to adjuvant therapy.

In the absence of lymph node involvement with negative seminal vesicles and Gleason score <8 disease, delayed biochemical recurrence (>1 year after surgery) predicts local recurrence. Hence, these patients may benefit from EBRT [31,32]. Both immediate and delayed adjuvant EBRT decrease PSA levels and produce modest improvements in 5-year biochemical progression-free survival rates [31,32], but no improvements in overall survival have been reported.

In summary, some positive surgical margins might be controlled locally with immediate or delayed adjuvant EBRT, but there is no evidence that adjuvant EBRT improves survival for this cohort, nor are there sufficient data to support early vs late adjuvant EBRT. To manage margin-positive patients, it is vital to review the pathology accurately, to determine the grade, location and extent of margins, and the status of seminal vesicles and lymph nodes. For example, systemic therapy (e.g. hormonal) should be considered in the presence of positive surgical margins with positive seminal vesicles, lymph nodes or a Gleason score of ≥7. However, adjuvant EBRT should be considered for biochemical recurrence >1 year after RP with a Gleason score of 2–6 and negative seminal vesicle and lymph node involvement, as this is more likely to reflect local recurrence.

CONCLUSIONS

The prevalence of positive surgical margins has declined steadily since the early 1990s. Explanations include a better understanding of pelvic anatomy, developments in surgical techniques, stage shift of the disease at presentation, and improved patient selection. Positive margins are predominantly apical and posterior, caused by capsular incisions, and do not appear to affect disease recurrence. However, a true positive margin increases the risk of progression, and therefore is an important factor for men undergoing RP. Despite the importance of margin status, other variables, including extraprostatic extension, seminal vesicle and lymph nodes status, and Gleason score, all affect the prognosis adversely, and must also be considered. At present, little consensus exists about the treatment of positive surgical margins, but there is some evidence that EBRT might benefit selected cases. Prospective randomized controlled trials comparing immediate vs delayed EBRT are required, as current studies have produced mixed results.

CONFLICT OF INTEREST

None declared.

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Abbreviations: EBRT, external beam radiotherapy; RP, radical prostatectomy; NVB, neurovascular bundle.
Hormonal therapy options for prostate-specific antigen–only recurrence of prostate cancer after previous local therapy

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KEYWORDS
PSA, prostate cancer, orchidectomy, LHRH agonist, maximum androgen blockade, bicalutamide

INTRODUCTION
The ‘PSA era’, which now spans >15 years (1988 to present), has dramatically altered the epidemiology of prostate cancer in the USA and many other industrialized countries. The incidence of prostate cancer peaked in the early 1990s, then decreased somewhat and is now rising again [1]. The American Cancer Society estimates that in 2004 there will be 230 110 newly diagnosed cases of prostate cancer in the USA [2]. Moreover, an increasing proportion of cases is being diagnosed at an earlier stage and in younger men, and these shifts have translated into changes in the pattern of prostate cancer treatment. Data from the USA Surveillance, Epidemiology and End Results (SEER) programme for 1985–97 show that the rate of radical prostatectomy (RP) increased from 8.0 per 100 000 men in 1985 to 47.8 per 100 000 men in 1992, and thereafter stabilized, and that the rate of radiotherapy use increased gradually over the entire period [1]. In 1997, RP and radiotherapy each accounted for the treatment of >30% of prostate cancer cases. Recently, a large USA military study showed a decline in the median age at RP to 62.3 years by 2000 and that >40% of men were <60 years old at the time of surgery [3].

In addition to its screening application, PSA can be used as a marker of early relapse, and one consequence of its use is the emergence of more men with PSA-only recurrence after definitive local treatment [4]. Assuming that about three-quarters of men with prostate cancer are treated with RP or radiotherapy, and that 30% of them will eventually have PSA recurrence, with >230 000 new cases diagnosed yearly in the USA, >50 000 men per year may be expected to develop PSA-only early progression.

The serum concentration of PSA used to define biochemical failure after treatment varies in published reports. For example, some RP series have used any detectable level, some a single value of >0.4 ng/mL or >0.5 ng/mL, and others two consecutive values of ≥0.2 ng/mL. A recent Mayo Clinic study of >2700 men found 0.4 ng/mL to be the most appropriate value to define treatable recurrence after surgery [5]. The 1997 American Society for Therapeutic Radiology and Oncology guidelines state that three consecutive increases in PSA constitute a reasonable definition of biochemical failure after radiotherapy [6].

Treatment of early progression marked by PSA-only recurrence after RP or radiotherapy (as opposed to adjuvant therapy applied to patients at high risk of failure immediately after radical therapy) is controversial. Clinicians, patients and their families are faced with decisions on whether treatment should be initiated immediately or deferred until there are signs and symptoms of clinical progression, and on the type of treatment to administer. Data suggest that a ‘risk-stratified’ approach to treating PSA recurrence may be the optimum strategy, with important factors including PSA doubling time during recurrence, Gleason sum and timing of recurrence [7,8]. For patients with a high likelihood of having organ-confined disease, localized therapies such as salvage surgery for recurrence after radiation, prostate-bed radiation for recurrence after surgery, and cryotherapy and brachytherapy may be appropriate. For patients with higher risk disease, e.g. those with a short PSA doubling time during recurrence, the initiation of androgen deprivation hormonal therapy is considered a reasonable approach [8].

To our knowledge, only one randomized trial of hormonal therapy (finasteride) for PSA-only recurrence has been completed. However, hormonal therapy is commonly used for PSA-only recurrence. Hormonal approaches in this setting have traditionally included surgical or medical castration and maximum androgen blockade (MAB; castration plus an oral antiandrogen), but unconventional approaches, e.g. antiandrogen monotherapy, are also increasingly being used.

This article reviews the evidence supporting the use of hormonal therapy for PSA-only recurrence, and presents a series of illustrative cases highlighting the possible benefits of monotherapy with the nonsteroidal antiandrogen bicalutamide 150 mg in this setting.

TRADITIONAL HORMONAL THERAPY
Androgen-ablation therapy with bilateral scrotal orchidectomy or MAB is the established approach in managing advanced metastatic prostate cancer. After the introduction of LHRH agonist therapy, the use of oestrogens declined because of their potential cardiovascular toxicity; however, there is some renewed interest in their possible use at low doses. Since the 1980s, investigators have evaluated MAB (with orchidectomy or LHRH agonist therapy plus an oral antiandrogen) as a means of improving the treatment outcomes achieved with testicular ablation therapy alone. However, there continues to be controversy about the efficacy of this approach. The latest meta-analysis data from the Prostate Cancer Trialists’ Collaborative Group study [9].
showed that MAB with the steroidal antiandrogen cyproterone acetate was associated with a significant reduction in 5-year overall survival of 2.8% relative to castration alone, whereas MAB with the nonsteroidal antiandrogens flutamide and nilutamide was associated with an improvement of 2.9%. Other meta-analyses [10–13] have shown varying improvements in overall survival with MAB compared with orchidectomy or LHRH agonist therapy alone, of up to 22% in a meta-analysis conducted by Caubet et al. [11]. Only one randomized trial has directly compared two nonsteroidal antiandrogens as components of MAB; a comparison of bicalutamide (50 mg once daily) with flutamide (250 mg three times daily), each combined with an LHRH agonist, in 813 men with metastatic disease [14]. Risks of death and progression were statistically equivalent between the treatment groups, although there were trends for longer overall survival (by >8 months) and a reduced risk of disease progression in the bicalutamide-treated patients. However, the flutamide-treated patients had a significantly higher incidence of diarrhoea (26% vs 12%, \( P < 0.001 \)) and more withdrawals because of it (25 vs two patients) than the bicalutamide-treated patients. Haematuria was significantly more common in the bicalutamide plus LHRH agonist group (12% vs 6% with flutamide plus LHRH agonist, \( P = 0.007 \)), but most cases were mild to moderate (81%) and there were no haematuria-related withdrawals.

No randomized trial to date has specifically evaluated traditional hormonal therapy in patients with PSA-only recurrence. Nevertheless, findings from studies of MAB in patients with minimal metastatic disease and comparisons of early and deferred hormonal therapy in patients with newly diagnosed disease or as adjuvant therapy suggest it is effective. Whether this benefit is transferable to the PSA-only recurrence setting is hotly debated.

Several studies have investigated the extent of disease as a prognostic factor for overall survival with MAB, and some [15,16], although not all [17], reported better survival benefits in patients with minimal metastatic disease. For example, a trial conducted by the US National Cancer Institute (NO) in 603 patients with metastatic prostate cancer showed a significant overall survival benefit for MAB with flutamide plus leuprolide vs placebo plus leuprolide, and analysis of data by extent of disease showed that the treatment difference was particularly evident in the subset of patients with minimal metastatic disease and normal performance status [15]. In this subset, there was a 19-month overall survival benefit in favour of flutamide over placebo. In contrast, a further NCI trial comparing MAB with flutamide plus orchidectomy vs placebo plus orchidectomy in 1387 patients with metastatic disease found no association between survival benefit for flutamide over placebo and extent of disease [17]. An exploratory analysis of data by extent of disease from the comparative study of bicalutamide plus LHRH agonist and flutamide plus LHRH agonist showed that patients with minimal metastatic disease treated by either regimen had a longer overall survival than those with extensive disease [16]. These findings suggest that patients with less extensive disease, such as PSA-only recurrence, may have better survival on MAB therapy than those with more extensive disease; however, the benefit of combined therapy in biochemical recurrence is purely speculative.

A trial conducted by the UK Medical Research Council directly compared immediate vs deferred hormonal therapy (with orchidectomy or an LHRH agonist) in 938 men with newly diagnosed locally advanced (M0) or asymptomatic metastatic (M1) disease [18]. There were significant advantages in favour of immediate treatment for reduced progression from M0 to M1 disease (\( P < 0.001 \)), reduced mortality from prostate cancer (\( P = 0.001 \); an effect enhanced in patients with M0 disease, \( P < 0.001 \)), and reduced overall mortality (\( P = 0.02 \)). A longer follow-up confirmed the advantage of immediate hormonal therapy in improving disease-specific survival, but there was a reduction in the overall survival difference, reflecting increased mortality from other causes [19]. The enhanced disease-related survival advantage in patients with M0 disease particularly supports the use of early hormonal therapy in patients with earlier stage disease, and this could include patients with PSA-only recurrence. However, the M0 patients in the study undoubtedly had more advanced disease than the average patient with PSA-only recurrence; moreover, some men in the deferred hormonal arm died before receiving any treatment and this may have biased results to an unknown extent in favour of early therapy.

A US Eastern Cooperative Oncology Group trial also reported significant benefits of immediate vs delayed hormonal therapy, with the LHRH agonist goserelin acetate or orchidectomy, in 98 patients who had RP but were found upon histological review to have pelvic lymph node metastases [20]. Immediate hormonal therapy showed advantages over delayed hormonal therapy for recurrence-free survival (\( P < 0.001 \)), disease-specific survival (\( P < 0.01 \)) and overall survival (\( P = 0.02 \)). At a median of 7.1 years of follow-up, the death rate from prostate cancer was 31.4% in the observation group, compared with only 6.4% in the immediate-treatment group; recurrence rates (including recurrence based on PSA levels) were 82.4% and 14.9%, respectively. As many patients (>60%) with PSA-only recurrence who have a ProstaScint® (Cytogen Corporation, NJ, USA) scan have pelvic and/or retroperitoneal adenopathy, extrapolation from this study to patients with PSA-only recurrence may be reasonable [4].

In a retrospective analysis of records from 1352 men in the USA who developed a biochemical recurrence (PSA >0.2 ng/mL) after RP and who had no other therapy, among those with high-risk PSA recurrence (PSA doubling time <1 year or Gleason score >7), early hormonal therapy administered at a PSA level of <10 ng/mL delayed metastatic progression compared with hormonal therapy deferred until PSA levels were higher [21]. A longer follow-up will be needed to determine if there is an effect on survival.

Tolerability is an important factor to consider in the decision of the timing of treatment in patients with PSA-only recurrence. For men who are relatively young and otherwise healthy, the benefits of early treatment with traditional hormonal therapy need to be balanced against side-effects of castration, which include decreased libido, impotence, hot flushes, anaemia, decreased muscle mass and a long-term risk of osteoporosis.

The actual PSA level at which immediate hormonal therapy is instituted is another factor to consider; should patients be treated when PSA is just detectable at 0.4 ng/mL, or at a higher level of 10, 20 or even 50 ng/mL? No randomized trial has evaluated whether treatment at lower PSA levels leads to greater prevention of further PSA relapse and improved survival.
DHT receptors and finasteride inhibits the antiandrogens act by blockade of cytoplasmic dihydrotestosterone (DHT); nonsteroidal prostate cancer growth are regulated androgen-dependent genes responsible for intracellular level in the prostate. The evaluated at the higher dose of 150 mg once.

Bicalutamide monotherapy was subsequently and subjective response rate [22]. 50 mg vs castration in the time to treatment with orchidectomy or LHRH agonist therapy open, randomized, multicentre comparisons has been the most extensively evaluated as such approaches are that patients may disadvantages over castration, including potential preservation of sexual function and fewer side-effects. The unconventional approaches are also less expensive than LHRH agonist therapy or MAB. The disadvantages of such approaches are that patients may experience breast tenderness and/or gynaecomastia, and that treatment is more expensive than observation or orchidectomy.

### UNCONVENTIONAL HORMONAL THERAPIES

Such hormonal therapy is currently receiving considerable attention for treating early PSA-only progression, with approaches including nonsteroidal antiandrogen monotherapy with bicalutamide or flutamide, 5α-reductase inhibitor therapy with finasteride or dutasteride, and combined nonsteroidal antiandrogen and 5α-reductase therapy.

Both the nonsteroidal antiandrogens and the 5α-reductase inhibitors exert effects at the intracellular level in the prostate. The androgen-dependent genes responsible for prostate cancer growth are regulated primarily by the testosterone metabolite dihydrotestosterone (DHT); nonsteroidal antiandrogens act by blockade of cytoplasmic DHT receptors and finasteride inhibits the intraprostatic conversion of testosterone to DHT by 5α-reductase. Both classes of agent inhibit the action of androgens from the adrenal gland, which account for ~9% of circulating androgens and are unaffected by castration, as well as from the testes, and they do not decrease serum testosterone levels. Their hormone responses translate into advantages over castration, including potential preservation of sexual function and fewer side-effects. The unconventional approaches are also less expensive than LHRH agonist therapy or MAB. The disadvantages of such approaches are that patients may experience breast tenderness and/or gynaecomastia, and that treatment is more expensive than observation or orchidectomy.

### ANTIANDROGEN MONOTHERAPY

**BICALUTAMIDE**

Of the available antiandrogens, bicalutamide has been the most extensively evaluated as monotherapy. Bicalutamide monotherapy was initially evaluated at a dose of 50 mg once daily in patients with metastatic prostate cancer, but an overview analysis of three open, randomized, multicentre comparisons with orchidectomy or LHRH agonist therapy showed a lower efficacy for bicalutamide 50 mg vs castration in the time to treatment failure, time to objective progression, survival and subjective response rate [22]. Bicalutamide monotherapy was subsequently evaluated at the higher dose of 150 mg once daily; it is not known whether this dose would be effective in PSA-only recurrence.

Two large phase III studies have compared bicalutamide 150 mg monotherapy with castration (orchidectomy or LHRH agonist therapy) in patients with M0 or M1 disease [23]. A combined per-protocol analysis found that in 805 M1 patients, at a median follow-up of 1.9 years, bicalutamide 150 mg was not as effective as castration, although the difference in median survival was only 42 days [24]. Post hoc analysis of these results showed that bicalutamide and castration had similar efficacy in patients with a pretreatment PSA level of ≤400 ng/mL, while survival data only favoured castration in patients with the highest tumour burdens at study entry (PSA > 400 ng/mL) [25]. In M0 patients, at a median follow-up of 6.3 years, there was no statistically significant difference between bicalutamide 150 mg and castration in overall survival or time to disease progression, but bicalutamide 150 mg offered quality-of-life advantages over castration, particularly in relation to physical capacity and sexual interest [23].

Two smaller ongoing trials are comparing bicalutamide 150 mg monotherapy with MAB using nilutamide plus orchidectomy or LHRH agonist [26], or flutamide plus LHRH agonist [27]. At a median follow-up of 32 and 38 months, respectively, these studies showed no significant survival differences between bicalutamide 150 mg and MAB.

Bicalutamide 150 mg once daily is also being evaluated as an adjuvant to standard care for patients with localized or locally advanced prostate cancer, in the ongoing bicalutamide Early Prostate Cancer (EPC) programme [28]. Studies using orchidectomy or LHRH agonist therapy provide evidence that adjuvant therapy given after radiotherapy for locally advanced disease [29,30] and in surgical patients with positive lymph nodes [20] can confer a survival benefit. The EPC programme involves 8113 men enrolled in three trials (conducted in different geographical areas) where patients were randomized to receive either bicalutamide 150 mg or placebo in addition to standard care (i.e. RP, radiotherapy or watchful waiting). At a median follow-up of 5.4 years there were benefits of bicalutamide 150 mg in patients with locally advanced disease [31]; among these men, bicalutamide significantly reduced the risk of objective progression compared with placebo by 29% in the RP subgroup (hazard ratio, HR 0.71; P = 0.0034), 42% in the radiotherapy subgroup (HR 0.58; P = 0.0035), and 47% in the watchful waiting subgroup (HR 0.53; P < 0.001). Overall survival was similar in the bicalutamide 150 mg and placebo groups in the overall population. However, in the watchful waiting subgroup, there was a trend towards improved survival with bicalutamide 150 mg in patients with locally advanced disease (HR 0.81; P = 0.097) but a trend towards reduced survival with bicalutamide 150 mg in those with localized disease (HR 1.23; P = 0.050). With bicalutamide 150 mg, the most common adverse events were gynaecomastia (68.3%) and breast pain (73.6%), and the withdrawal rate because of these adverse events was 16.7%. Fewer patients with locally advanced disease withdrew from bicalutamide 150 mg because of gynaecomastia and/or breast pain (12.9%) than those with localized disease (18.6%). Other adverse events occurred with a similar low incidence to that in the placebo group. Bicalutamide 150 mg once daily has not yet been extensively evaluated in the setting of PSA-only recurrence.

### FLUTAMIDE

Published data on the efficacy of flutamide monotherapy are inconclusive. Results from one small study of 92 patients with advanced disease showed that flutamide was less effective than diethylstilbestrol in the time to clinical treatment failure (9.7 vs 29.7 months) and overall survival (28.5 vs 43.2 months) [32], while results of two larger studies comparing flutamide with MAB or orchidectomy alone found no differences in clinical progression-free or overall survival [33,34].

An open randomized controlled trial of adjuvant flutamide 250 mg three times daily after RP in 309 patients with pT3 disease showed that, at a median follow-up of 6.1 years, flutamide significantly improved recurrence-free survival compared with no adjuvant therapy (HR 0.51; P = 0.0041) [35]. However, there was no treatment difference in overall survival (P = 0.92), and there was considerable toxicity reported in the flutamide group, including gastrointestinal toxicity and hepatotoxicity.

Flutamide 250 mg daily for PSA-only recurrence is currently being investigated, but no results are available at present (Moul et al. personal communication).
5α-REDUCTASE INHIBITORS

To our knowledge, the only randomized trial to date conducted in the PSA-only recurrence setting was a comparison of oral finasteride 10 mg daily vs placebo in 120 men with PSA-only recurrence (PSA levels of 0.6–10.0 ng/mL) after RP [36]. Patients received either finasteride or placebo for a year and all then received finasteride for a further year. Finasteride was well tolerated and delayed increases in PSA levels compared with placebo by >9 months in the first year and 14 months by the end of the second. However, recurrence rates (defined as clinical progression or PSA level increased by >10 ng/mL from baseline) were not statistically significantly different between finasteride and placebo at either 1 or 2 years.

COMBINED THERAPY

Two small unrandomized studies evaluated the combination of finasteride and flutamide in men with early progression detected by PSA only [37,38]. One study evaluated finasteride 5 mg twice daily combined with flutamide 125 mg twice daily in 71 men with PSA-only recurrence after RP or external-beam radiation [38]. The mean PSA at the start of treatment was 15.2 ng/mL. A PSA nadir of <0.1 ng/mL was achieved in 58% of patients and the mean time to PSA nadir was 7.9 months. Twenty-one patients subsequently experienced failure; of these, only six (28%) had a PSA nadir of <0.1 ng/mL. Adverse events in the study included breast tenderness (50%), breast enlargement (72%), gastrointestinal disturbances (22%) and fatigue (10%). In a second study evaluating the same doses in 36 men with PSA-only recurrence after RP or external-beam radiation, 42% of patients had a PSA nadir of <0.1 ng/mL and the mean time to nadir was 4.7 months [37]. These studies suggest that a randomized phase III trial of such combined therapy in patients with early progression is warranted.

The use of bicalutamide 150 mg or a lower dose combined with a 5α-reductase inhibitor in patients with PSA-only recurrence has not yet been investigated.

CASE HISTORIES

In light of the results from the bicalutamide EPC programme [31], some men have elected to receive bicalutamide 150 mg once daily for PSA-only recurrence of prostate cancer after previous local therapy. In general, these men have wanted to avoid the side-effects associated with traditional hormonal therapy but recognize that such therapy may ultimately be required.

PATIENT 1

Although this 55-year-old company executive was in otherwise good health, he presented with a PSA level of 69 ng/mL and was clearly in need of urgent appraisal for prostate cancer. A DRE indicated clinical T3 disease and there was a very high probability of micrometastases. All scans were negative but six positive biopsies confirmed the diagnosis of a high-grade tumour, Gleason sum 8. Hormonal therapy was initiated immediately, and 9 months of LHRH agonist therapy was successful in reducing his PSA level to 0.5 ng/mL; however, it was never undetectable. During subsequent months his PSA level increased to 0.9 ng/mL. After long discussions between the patient and colleagues, and despite the high likelihood of micrometastases, this young patient selected RP, after which his PSA was undetectable for 6 months, but then increased again. Although the rate of PSA increase was indicative of distant failure, the patient opted for a course of radiotherapy, after which his PSA was undetectable for 6 months. This time his bone scan was negative but CT and ProstaScint scans revealed mesenteric adenopathy. After exhaustive Internet searches, consultations with physicians and support-group sessions, the patient chose to begin antiandrogen monotherapy (bicalutamide 150 mg once daily), with prophylactic breast irradiation to prevent breast tenderness and gynaecomastia. After 6 months, the patient’s PSA had decreased to 0.02 ng/mL and his only side-effect was a mild abnormality on a liver function test. Because of this, the patient elected to discontinue bicalutamide monotherapy and start LHRH agonist therapy with goserelin acetate. His PSA level remains undetectable.

PATIENT 2

This 65-year-old man was diagnosed with prostate cancer in 1993; his PSA level was 23 ng/mL, and he had clinical T2c disease and Gleason sum 8 (4 + 4). Bone and pelvic CT scans were negative. The patient chose external-beam radiation therapy (69 Gy), which was successful in reducing his PSA level to 0.59 ng/mL in July 1994; however, he had poor erections after treatment. During subsequent years, his PSA level increased from 0.72 to 4.5 ng/mL. Bone scans and pelvic CT were negative but repeated prostate biopsies revealed evidence of high-grade disease (Gleason sum 8). As the patient wished to maintain his libido and have a penile prosthesis, he selected antiandrogen...
monotherapy (bicalutamide 150 mg once daily), with prophylactic breast irradiation to prevent breast tenderness and gynaecomastia. During subsequent months, this sexually active older man maintained his strong libido; had no breast symptoms and now has a new penile prosthesis. As of October 2003, his PSA level was 0.42 ng/mL.

SUMMARY
Prostate cancer recurrence that is detectable only by a rise in PSA level after successful local treatment for prostate cancer is a very common problem facing patients and their clinicians. Recent studies suggest that early hormonal therapy provides a survival benefit in patients with M0 disease and after RP in patients with pelvic lymph node metastases; however, the survival benefit for PSA-only recurrence has yet to be confirmed. As shown by the case histories presented here, unconventional hormonal therapy, e.g. antiandrogen monotherapy, appears to be a reasonable option. The potency-sparing potential of this approach is appealing, as is the reduced degree of other side-effects associated with traditional hormonal (castration) therapies, but the long-term efficacy in patients with early PSA-only progression is unknown. The possibility of breast symptoms during antiandrogen monotherapy may be reduced with the use of prophylactic low-dose breast irradiation. More clinical trials are needed to determine the best treatments, alone and in combination, for these patients.

CONFLICT OF INTEREST
Judd W. Moul is a consultant to Astra-Zeneca.

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Abbreviations: RP, radical prostatectomy; DHT, dihydrotestosterone; EPC, early prostate cancer; HR, hazard ratio; MAB, maximum androgen blockade; NCI, National Cancer Institute; SEER, Surveillance, Epidemiology and End Results.
Hypoactive sexual desire disorder: an underestimated condition in men

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KEYWORDS
male hypoactive sexual desire disorder, erectile dysfunction

INTRODUCTION
One consequence of the availability of medication that allows men to enhance their erection is that male hypoactive sexual desire disorder (HSDD) is erroneously presented and treated as erectile dysfunction (ED). The lack of public education on sexual health issues, the myth that men are always motivated to be sexual, insufficient sexological knowledge of health-care providers, and the lack of tools to comprehensively assess male HSDD, are causative factors of this misconception, which may partly explain the high proportion of failures of treatments for symptomatic ED. In population-based studies HSDD has been reported in 0–15% of men, and ED in 10–20% [1]. Recently, Simons and Carey [2] analysed 52 studies published between 1990 and 2000; community samples indicate a prevalence of 0–5% for ED and 0–3% for male HSDD, while prevalence estimates from primary-care and sexuality clinic samples are characteristically higher. With the aim of putting HSDD on the agenda of providers of male sexual healthcare, here we review publications on the pathophysiology of male HSDD, and its biological and psychological correlates.

According to the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) classification, HSDD is the persistent or recurrent absence or deficit of sexual fantasies and desire for sexual activity, accounting for factors that affect sexual function, e.g. age, sex and life context (http://www.psychnet-uk.com/dsm_iv/hypoactive_sexual_desire_disorder.htm).

Although many studies have been conducted, especially of female HSDD, the lack of methodological rigor of many studies limits the confidence in the findings [2]. HSDD is currently recognized as the most difficult sexual disorder to operationally define, evaluate and treat.

THE ASSESSMENT OF SEXUAL DESIRE AND DESIRE PROBLEMS
HSDD is associated with a wide variety of biological and psychological causes [1]. At present, no single instrument for diagnostically assessing HSDD prevails [3]. Sexual healthcare providers who wish to be alert to a diagnosis of HSDD are advised to pose direct and unambiguous questions to their patients, to probe for aspects of sexual desire and motivation. Patients often will not reveal sexual problems unless explicitly invited [4]. Collateral information may be obtained through questionnaires, completed before or after the consultation. Several reliable and valid questionnaires are available for assessing sexual desire problems, with easy-to-follow instructions. The Sexual Desire Inventory [5] was designed specifically to measure level of sexual desire, the International Index of Erectile Function [6] provides a subscale to measure sexual desire, and the Golombok Rust Inventory of Sexual Satisfaction [7–9] provides subscales of sexual avoidance, and of infrequency of sexual contact.

THE INTERFACE BETWEEN BIOLOGY AND PSYCHOLOGY OF MALE SEXUAL DESIRE
The investigation of male sexual behaviour has been greatly influenced by Beach’s concept of the ‘dual nature of sexual arousal and performance’, derived from his extensive research on male rats [10]. He postulated that sexual behaviour depends on two, relatively independent, processes controlling motivation and consummation. Motivation involves a sexual arousal mechanism that determines a male’s sexual response to perception of a receptive female. Its main function is to stimulate the male rat to approach a female and to raise his sexual excitement to the threshold necessary for consummatory elements of sexual behaviour, i.e. mounting and intromission. Thereafter, the consummatory mechanism controls the intromission and ejaculatory elements of the male rat’s sexual behaviour, integrating the sequence of mounts and intromissions, thus amplifying the male’s arousal until ejaculation occurs. Recent animal research has expanded Beach’s model [10], and, for instance, motivational and consummatory processes have been shown to involve separate brain regions [11], independently modulated by androgenic and dopaminergic agents [12–14]. Animal studies suggest that an intricate interplay between steroid hormone actions in the brain maintains central sexual arousability and the organism’s individual experience with sexual gratification. From this, expectations of competent sexual functioning have been developed, including sexual activity, sexual desire, arousal and sexual performance. However, the validity of extrapolating findings to human sexual functioning remains to be evaluated in empirical studies. Recent work in neurobiology has allowed conceptualisations of sexual motivation and performance, the complexity of which far exceeds the models based on Beach’s concept.

The linear model of the human sexual response as postulated by Masters and Johnson [15] has dominated clinical research for several decades. This model omitted sexual desire and problems of hypoactive desire completely, probably because Masters and Johnson studied individuals who were highly motivated to engage in sexual activity. Later authors added the concept of sexual desire, but still adhered to the linear model, proposing that sexual desire is needed to initiate subsequent sexual arousal and orgasmic release [16–18]. They considered the presence of sexual thoughts and fantasies, and an innate urge to experience sexual tension and release, as markers of desire [18]. Over time, the linear model of the sexual
response acquired normative properties, prescribing that the personal experience of lustful desire in both sexual partners should precede any initiation of sexuality. However, real-life experiences of numerous ‘steady’ couples show almost universal differences in the experience of sexual desire between partners, regarding both timing and frequency of sexual activity, and sometimes giving rise to serious marital conflicts. Moreover, humans engage in sexual contacts for countless motives, only one of which is the awareness of an intrinsic urge for sexual activity. Many motives are not sexual, such as pleasing or appeasing a partner, banishing gloomy thoughts, chasing away boredom, or monetary or other material rewards. Recognition of this gave rise to the notion of a ‘receptive sexual desire’, as opposed to ‘active desire’ [19].

Thus the linear model of sexuality gave way to circular or multifactorial hypotheses regarding the interrelationships of sexual desire, arousal and performance, and the influence of unconscious, involuntary and automatic processes, along with conscious motives and deliberations, was recognized. Building on new findings from neuroscience, Janssen et al. [20] proposed a two-stage information-processing model of sexual arousal, based on the concepts of ‘the multiplicity of meaning of sexual stimuli’ and of ‘the interaction of automatic and controlled processing’ of such information. According to this model, in the first stage, subliminal stimuli render the sexual system receptive to sexual stimuli, and prepare the organism to respond with physical arousal [20,21] (Fig. 1). Many psychological and biological factors might preclude the deployment of the genital sexual response, but if processing of stimuli in the limbic centres is such that some degree of arousal is experienced, the individual can continue to focus on sexual stimuli. Depending on the unconscious processing of either the mere erotic meaning of the sexual stimuli, or of many meanings, including negative valence (particularly in sexually dysfunctional men), further arousal might follow in the second stage. After the priming-based and unconscious motivational engagement, the man may become aware of this motivation as a desire to continue the experience for the sake of the sexual tension and enjoyment. In this cycle, sexual stimuli can be processed at a pre-attentive level, and arousal can be experienced before desire.

Mental sexual arousal alters the descending neurotransmission from limbic centres to the lumbar sacral centres of the spinal cord. There is evidence that this involves increasing oxytocinergic signalling from the paraventricular nuclei of the hypothalamus, with concurrent reduction of inhibitory serotonergic input, particularly from the nucleus paragigantocellularis in the medulla [22]. When this balance of signalling to the pelvic autonomic outflow occurs, the subsequent physical tumescence constitutes an additive or compounding second-level sexual stimulus. The engorgement is usually accurately detected and enjoyed. Men with chronic situational ED typically underrate their physical response [23], whereas sexually functional men have higher correlations between genital and subjective measures of arousal. In contrast, in women these measures tend to show little overlap [24,25].

Psychophysiological data of objective increases in vaginal blood flow (in the laboratory) in response to erotic stimulation consistently show no correlation with the female’s subjective arousal [26,27]. Thus, women may not have this direct confirmation of their genital arousal, which might explain why many women need direct stimulation of their congesting vulvar structures for the second level confirmatory stimulus. Clearly, some sexual styles, particularly intercourse-focused, may preclude this.

Although the two-stage model remains to be validated by empirical testing, it may guide the present discussion of sexual desire problems in men. The most prominent implications of the Janssen et al. [21] model are: (i) the unconscious and automatized initiation of genital response preparation upon (subliminal) perception of erotic stimuli; (ii) the nonlinear relationship between sexual desire and sexual arousal, implying the possibility of sexual arousal preceding desire; and (iii) the possible inhibitory effect of
mental preoccupation and non-sexual thoughts on both desire and arousal.

TESTOSTERONE AND PROLACTIN

It is not clear whether the neural circuits involved in sexual desire operate in parallel or in series to orchestrate the normally integrated pattern of sexual behaviour, i.e. appetitive responses that enable a male to gain close proximity with a female in heat so that the reflexive and stereotyped pattern of copulatory responses can occur. Importantly, extensive studies have shown that testosterone is necessary for the full range of sexual responses [28,29]. The physiological range of testosterone concentrations (3-12 ng/mL) is considerably higher than necessary for normal sexual function. Critical testosterone levels for sexual function in males are ~3 ng/mL, but with large inter-subject variation [30], whereas levels at which androgen-related sexual behaviour in men declines appear to be reproducible [31]. In patients with induced or spontaneous hypogonadism, either pathological withdrawal and re-introduction of exogenous androgens affects the frequency of sexual fantasies, sexual arousal and desire, spontaneous erections during sleep and in the morning, ejaculation, sexual activities with and without a partner, and orgasms through coitus or masturbation.

There is only limited evidence on the effects of testosterone administration to eugonadal men with or without sexual problems, but in a controlled study of eugonadal men with diminished sexual desire, O’Carroll and Bancroft [32] showed that injections of testosterone esters produced a significant increase in sexual interest compared to placebo injections. However, in most of the men studied, the increase in sexual interest was not translated into an improvement of their sexual relationship, perhaps because psychological problems with their partner had not been resolved with hormonal treatment only. When supra-physiological doses of testosterone were administered to healthy volunteers as a potential hormonal male contraceptive, this resulted in a significant increase in psychosexual stimulation or arousal, but there were no changes in sexual activity or spontaneous erections [33]. As healthy males produce much more androgen than necessary to maintain sexual function, lowering serum testosterone levels to the normal low range, or increasing them to the high normal range in eugonadal men, has no appreciable effect on sexual function. This leads to the conclusion that androgens are only beneficial in men whose endogenous levels are abnormally low. However, O’Carroll and Bancroft [32] indicated that, with increasing levels of endogenous androgen supply, it becomes more difficult to manipulate circulating levels with exogenous hormones. The homeostatic mechanisms are powerful, and the more the testosterone is administered, the more the endogenous supply is suppressed or the metabolic clearance rate is increased [34]. Benkert et al. [35] delivered testosterone undecanoate daily to treat ED in eugonadal men, but achieved no increase in circulating hormone levels. Their failure to produce any behavioural effect on erectile function therefore may not be a result of ineffective androgens, but of a failure to alter hormone levels.

Indeed, a significant relation between physiological androgen levels and male sexual behaviour has been observed in several studies. In a Swedish epidemiological investigation of 500 men aged 51 years, low levels of free testosterone were associated with low sexual interest [36]. In young soldiers aged 18–22 years, serum concentrations of 5α-dihydrotestosterone were a significant determinant of orgasmic frequency [37]. In young healthy volunteers, Knusmann et al. [38] showed positive correlations of salivary and total serum testosterone levels with the frequency of orgasms. Most intra-individual correlation coefficients were also positive, but some were negative or insignificant, indicating the great intra- and inter-individual variability of behavioural responses to hormones, which might explain contradictory results from other studies on testosterone levels and frequency of orgasm.

Hyperprolactinaemia may be a cause of hypogonadism and therefore lead to HSDD. Moreover, the neuroleptic activity of prolactin itself may lead to depression and anxiety in conjunction with HSDD [39].

PSYCHIATRIC CONDITIONS

Relationship difficulties are often encountered as comitant to HSDD. The cause-effect relationship is sometimes hard to disentangle, especially if the problem has a long history. It might often be difficult for a man to admit that his lack of sexual desire is associated with his dissatisfaction with the relationship, or with resentment towards his partner; masculine myths in many cultures hold that men are always ready to engage in sexual activity, even in unfavourable conditions, or imply that a lack of desire for sex with his partner reflects the man’s waning love for her. Subtle cases of relationship discord require meticulous history-taking, sometimes including the scheduling of visits to a physician without the partner being present. Anger may be an important mechanism through which sexual desire and arousal are inhibited [40]. For women, both anger and anxiety significantly reduce desire, with anger showing the more marked effect. For men, similar results have been noted, although with fewer differences reported between the anxiety and anger conditions. Significantly more women than men indicate that they would terminate a sexual activity during anger [41].

HSDD is the most frequent form of sexual disorder experienced by psychiatric outpatients. Underlying causes are multifactorial in most cases. The patients most frequently affected are schizophrenics on neuroleptic medication, whereas schizophrenic patients on no medication have fewer dysfunctions [45]. Major depression is associated with decreased sexual interest in >40% of men [42,43], although Bancroft et al. [44] found that the depressive effect was associated with an increase in sexual desire in 9% of a group of heterosexual men. It remains unclear how these differential effects are mediated. Sexual dysfunction commonly occurs during antidepressant treatment. Although depressed patients care about their sexual function, they may be reluctant, for fear of embarrassment, to report HSDD spontaneously to their physicians. HSDD is probably under-reported and may result in covert non-compliance and relapse into depression. Physicians thus need to assess sexual function during the initial evaluation and throughout treatment. The importance of sexual function to sexually active patients with major depression should be considered carefully when planning antidepressant therapy. Viable options exist to prevent or treat HSDD, including use of relatively new antidepressants and appropriate adjunctive regimens [46].

Improvement in sexual functioning related to antidepressant effects may be more common
than drug-associated deterioration in sexual function. Among patients who report worsening, the effects may be most pronounced on orgasm. Deterioration in sexual function does not appear to be a late-onset, drug-specific event, but is strongly related to worsening depressive symptoms [47]. Moreover, the reported rates of sexual dysfunction vary with the antidepressant used and are typically under-reported in product literature. Tricyclic antidepressants, selective serotonin reuptake inhibitors and venlafaxine XR are associated with higher rates of sexual dysfunction than bupropion or nefazodone [48,49]. As physicians considerably underestimate antidepressant-associated sexual dysfunction, greater recognition and education are imperative when prescribing antidepressants [50].

MEDICAL CONDITIONS

Although not a medical condition, ageing is the most significant risk factor for HSDD. In men aged >40 years there is a gradual, often imperceptible decrease in sexual desire, but although ageing men do not usually experience the strong sexual interest characteristic of youth, most report continued interest from a mild to moderate degree [51]. However, HSDD is frequently experienced by patients with chronic medical conditions, e.g. coronary disease and heart failure [52], renal failure and HIV. For example, 71% of HIV patients report some degree of sexual dysfunction after beginning their treatment, of whom 89% report decrease or loss of libido [53]. HSDD, subjectively ascribed to fatigue, is also common among patients with chronic renal failure [54]. Men on haemodialysis or peritoneal dialysis suffer significantly more renal failure [54]. Men on haemodialysis or peritoneal dialysis suffer significantly more from HSDD than men with kidney transplantation or rheumatoid arthritis. Diemont et al. [55] reported a HSDD prevalence of 56% in men on haemodialysis, 48% in men on peritoneal dialysis and 41% after renal transplantation.

Hyperactive sexual desire is a known, although not frequently recognized, side-effect of dopaminergic anti-Parkinson therapy, especially levodopa. This side-effect is not life-threatening but can have an enormous impact on the quality of life of the patient, and his or her partner. The mechanism is probably related to the pharmacological action of dopamine [57,58]. Bipolar (manic-depressive) affective disorder is also associated with hypersexual desire, specifically in manic episodes, and lithium treatment has been found to reverse the sexual symptoms of this condition.

Although hyposexuality is a common problem in stroke patients, some may present with hypersexuality [59]. Patients with isolated symmetric damage to the amygdala and their cortical connections show marked behavioural changes, including visual agnosia, hypersexuality, hyper-orality, a tendency to react to every visual stimulus, and memory deficits. The cluster of neurobehavioural symptoms is similar to previously reported accounts of Kluver–Bucy syndrome, and suggests the importance of bilateral amygdala involvement in these changes [60].

Lack of sexual desire is reported significantly more often by both bodybuilders and men with eating disorders than by controls [56]. Bodybuilders show a pattern of eating and exercising as obsessive as that of subjects with eating disorders, but with a ‘reverse’ focus of gaining muscle, as opposed to losing fat.

CONCLUSION

HSDD is associated with a wide variety of biological and psychological causes (Appendix) [61,62]. The vast array of physical and mental events and agents capable of producing HSDD reflects the fragility of human sexual desire. Uncompromised sexual motivation apparently requires a delicate balance between physical and psychological systems. The apparent fragility of sexual desire has evoked the metaphor of a ‘final common pathway’. However, this seems to have discouraged research to identify the commonality of different causative factors and the interrelationships. For example, no experimental research has, to our knowledge, compared the subjective and psychophysiological arousability of individuals with and without HSDD. For the therapeutic management of HSDD, either pharmacological or psychological treatments have been tested, but factorial designs were used to investigate the differential contributions and interactions of both approaches have not been reported. Information processing models (e.g. Janssen et al. [20]) may give a new impetus to research that crosses traditional disciplinary boundaries by emphasising the simultaneous operation of biological and psychological factors in the generation and modulation of sexual functioning aspects of desire and arousal.

HSDD is more common in men than in women. In public opinion and in medical practice, HSDD is often misinterpreted as ED, and treated as such. There is a need for physicians and patients to be educated, and for the development of reliable clinical tools to assess this aspect of male sexual function.

CONFLICT OF INTEREST

None declared.

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Abbreviations: ED, erectile dysfunction; HSDD, hypoactive sexual desire disorder.

APPENDIX

Psychological and biological factors in HSDD

Contributing factors
Androgen deficiency
Hyperprolactinaemia
Anger and anxiety
Depression
Relationship conflict
Stroke
Antidepressant therapy
Epilepsy [61]
Post-traumatic stress syndrome [62]
Renal failure
Coronary disease and heart failure
Ageing
HIV

Body-building and eating disorders
Conventional and alternative methods for providing analgesia in renal colic

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INTRODUCTION

Renal colic secondary to a ureteric calculus produces one of the most severe forms of pain known to man, and yet the ideal analgesia remains unknown. In this article we review currently available analgesics and summarize possible alternatives for this condition.

The pain of renal colic is thought to be related to ureteric smooth muscle spasm, oedema and inflammation at the level of the calculus, and increased peristalsis and pressure proximal to the calculus. Persistent obstruction of the urinary tract may lead to renal impairment secondary to prostaglandin release as part of the inflammatory response. Within hours, the pressure gradient across the glomerulus equalises as pelvic pressure increases. In response, glomerular filtration and renal blood flow reduce. Unless the obstruction is relieved, renal impairment ensues.

The most effective pain relief for patients with complete ureteric obstruction is relief of the obstruction by spontaneous passage or removal of the calculus, or by placing a stent or percutaneous nephrostomy.

Fortunately, most patients do not have complete obstruction and so are not at imminent risk of renal impairment. Expectant management is appropriate in the majority and, for these patients, pain management is most important. As the pain of renal colic is related in part to increased ureteric muscular activity, drugs able to relax the smooth muscle may be the most effective analgesics. These drugs also appear to be effective at facilitating spontaneous stone passage, when used in randomized clinical trials [1–3].

KEYWORDS

calculus, renal colic, analgesia, nifedipine, calcium channel blockers, alpha blockers,

CONVENTIONAL ANALGESICS

Opioid analgesics and NSAIDs remain the mainstay of treatment for acute renal colic. Opioid analgesics, e.g. morphine and pethidine, are highly effective during the acute episode. Various preparations are available but the intravenous form has the most rapid onset of action and the advantage that the dose may be titrated to effect. However, prolonged use may cause dependence and tolerance. Side-effects are common, including nausea, vomiting, constipation and drowsiness, and larger doses can cause respiratory depression and hypotension. The data are conflicting for the effect of opiates on ureteric tone; results generally indicate an increase or no effect [4]. Ideally, an alternative to opiates would be preferred, as increased ureteric tone is thought to be counterproductive in acute renal colic and the side-effects of opiates can be problematic.

Codeine and dihydrocodeine are less potent opioids than morphine; they are effective for relieving mild to moderate pain. Constipation is a significant side-effect and limits long-term use. Dextropropoxyphine is half as potent as codeine and is often given in combination with paracetamol (coproxamol) for mild pain when other opioids are contraindicated. There is little evidence that such combinations are more effective than paracetamol alone.

Tramadol is an opioid analgesic with fewer opioid side-effects, notably less respiratory depression, constipation and potential for addiction. Intravenous, intramuscular, subcutaneous and oral preparations are available. Tramadol is as effective as morphine for moderate postoperative pain but it does appear to be less effective for severe acute pain. Common adverse effects include dizziness, nausea, dry mouth and sedation. When used for treating renal colic, tramadol 100 mg has been shown to be as effective as pethidine 50 mg [5]; the percentage of patients halving their pain intensity with tramadol 100 mg and pethidine 50 mg after 15 min was, respectively, 43% and 47%, and after 30 min, 83% and 90%. Tramadol requires more research but may prove to be a suitable alternative to conventional opioids.

NSAIDs are known to be as effective as opioids at relieving the pain of acute renal colic. Although those receiving morphine report more pain relief at 10 min, there is no significant difference by 20–30 min [6]. The analgesic action of NSAIDs results from the inhibition of prostaglandin synthesis (Fig. 1). This prevents the afferent arteriolar vasodilatation and increased vascular permeability which promotes a diuresis and raises renal pelvic pressure. It also reduces oedema, inflammation and ureteric muscular overactivity.

There are many NSAIDs available; the main differences between them are the incidence and type of side-effects, predominantly gastrointestinal irritation and ulceration. Ibuprofen has the fewest side-effects and the lowest risk of gastrointestinal effects, but has the weakest analgesic action. Naproxen and diclofenac provide stronger analgesia with a low incidence of side-effects. Indomethacin is equipotent to naproxen but with a higher incidence of side-effects, including headaches, dizziness and gastrointestinal disturbances. Oral diclofenac and oral/rectal indomethacin have both been shown to be effective at reducing the number of new colic episodes and further admissions to hospital, but they have no effect on spontaneous stone passage rates (Table 1) [7,8].

Intravenous preparations available include diclofenac, tenoxicam and lornoxicam. These have the fastest onset of action but this is accompanied by a higher risk of side-effects (Table 2) [9], including nausea, vomiting, a sensation of heat or tension across the chest, giddiness, tiredness and general malaise.

Previous studies have reported tenoxicam to be as effective as pethidine in managing acute renal colic, but the onset of action of tenoxicam is slower than pethidine and therefore, for persistent severe pain, a combination of tenoxicam plus a faster acting drug, such as pethidine, has been suggested.

NSAIDs effectively reduce pain but potentially they interfere with the renal autoregulatory response to obstruction by decreasing renal blood flow [10]. This is well tolerated in healthy individuals, but renal failure may be induced in those patients with pre-existing renal disease. Dehydration secondary to vomiting may also contribute. In patients with cardiac disease, there is a risk of promoting heart failure and cardiac decompensation [11].

NSAIDs vary in their selectivity for inhibiting different types of cyclooxygenase (COX). Selective inhibition of COX II improves gastrointestinal tolerance but still has a detrimental effect on renal and cardiac function in those with pre-existing disease. COX II is present in most cells, including the gastric mucosa, but at low levels. Typically, COX II is upregulated locally in response to an inflammatory stimulus, and therefore drugs able to selectively inhibit COX II should limit their effects to the affected area. Selective COX II inhibitors have been suggested to be a suitable alternative to NSAIDs and include celecoxib and parecoxib. Although COX II inhibition reduces ureteric contractility as effectively as indomethacin in porcine and human ureteric segments in vitro, there are currently no data available on its use in treating renal colic. The effect of COX inhibition on the rate of spontaneous ureteric contraction in vitro by indomethacin (nonselective COX inhibitor) and NS398 (selective COX II inhibitor) vs a DMSO control showed a reduction of 100%, 100% and 20%, respectively in a mean of 29, 21 and >150 min [12].

Currently available COX II inhibitors are orally administered; this may not be suitable for most patients with renal colic because of the delayed onset of action and the inability of many to tolerate oral medications. The delayed action of many orally administered drugs emphasizes the need for combined treatment in many cases of renal colic.

**ALTERNATIVE DRUG THERAPY**

Antimuscarinic drugs are useful for treating smooth muscle spasm, predominately gastrointestinal. Within the genitourinary system the autonomic nervous system modulates ureteric activity by controlling peristaltic frequency [13]. Hyoscine butylbromide (buscopan) is an antimuscarinic drug which has been shown, using a non-occlusive ureteric catheter, to decrease human ureteric activity in vivo to some degree in 80% of subjects [14]. Unfortunately, these drugs are associated with significant side-effects, including dry mouth, facial flushing, dryness of the skin, photophobia, loss of accommodation, urinary urgency and retention, and constipation, and so their use is limited in renal colic.

Drotaverine, a phosphodiesterase IV inhibitor, has an antispasmodic action without the antimuscarinic side-effects. It is currently used successfully in many countries for treating renal colic. A multicentre, placebo-controlled, randomized, double-blind study used drotaverine to control the acute episode on arrival to hospital [15]; drotaverine provided effective analgesia in 79% of patients (as compared with 46% receiving placebo). There were no serious side-effects. Frequent minor side-effects included nausea, vomiting, vertigo and a transient decrease in blood pressure.

**TABLE 1** Published results; NSAIDs for the prophylaxis of acute renal colic

<table>
<thead>
<tr>
<th>Mean variable</th>
<th>Diclofenac*</th>
<th>Placebo</th>
<th>Indomethacin†</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stone size, mm</td>
<td>78% &lt; 6</td>
<td>97% &lt; 6</td>
<td>2.9</td>
<td>2.8</td>
</tr>
<tr>
<td>Stone passage rate, %</td>
<td>68 &lt; 3 weeks</td>
<td>74 &lt; 3 weeks</td>
<td>59 &lt; 1 week</td>
<td>61 &lt; week</td>
</tr>
<tr>
<td>Interval to passage, days</td>
<td>28</td>
<td>29</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Readmission rate, %</td>
<td>10</td>
<td>67</td>
<td>11</td>
<td>39</td>
</tr>
</tbody>
</table>

*50 mg three times daily for 7 days; placebo same; †25 mg twice daily + rectal 100 mg at night for 7 days; placebo the same.

**TABLE 2** The mean pain score (as a percentage of that before treatment) after 50 mg intravenous or 100 mg rectal indomethacin

<table>
<thead>
<tr>
<th>Time (min) from administration</th>
<th>Intravenous</th>
<th>Rectal</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>54</td>
<td>73</td>
</tr>
<tr>
<td>20</td>
<td>29</td>
<td>50</td>
</tr>
<tr>
<td>30</td>
<td>16</td>
<td>29</td>
</tr>
<tr>
<td>Side-effects, %</td>
<td>55</td>
<td>37</td>
</tr>
</tbody>
</table>

*50 mg three times daily for 7 days; placebo same; †25 mg twice daily + rectal 100 mg at night for 7 days; placebo the same.
Isosorbide dinitrate has been used in clinical trials when used to treat renal colic. Many cardiovascular drugs, known to exert their action by relaxing vascular smooth muscle, are showing promising results in clinical trials when used to treat renal colic. Isosorbide dinitrate has been used in combination with the NSAID tenoxicam in the acute management of renal colic, and found to augment the analgesic effect offered by tenoxicam alone [16]. 40 mg of tenoxicam alone (control group) decreased the mean visual analogue pain score from 90/100 to 38/100. Adding 5 mg of sublingual isosorbide dinitrate (treatment group) improved the pain score from 84/100 to 22/100 (P < 0.05). Sublingual isosorbide dinitrate has a rapid onset of action within 2–5 min of administration. It stimulates the release of nitric oxide, leading to vascular smooth muscle relaxation. Nitrates can have the same effect on ureteric smooth muscle, but unfortunately they have a short duration of action and problematic side-effects (flushing, headache, postural hypotension). They may prove to be a useful adjuvant treatment with those analgesics that have a delayed onset of action.

To date, there are no reported clinical trials to assess the effect of isosorbide dinitrate used in isolation. However, glycerol trinitrate (GTN) patches have been used [17]. Patients with calculi of <10 mm in diameter were randomized to receive a 6-week course of patches containing either 5 mg GTN or placebo. At the end of the this period the GTN group reported fewer pain episodes (median 3.5 vs 6.0), but this was not statistically significant. Furthermore, 27% of patients receiving GTN had to discontinue therapy because of headaches.

Calcium-channel antagonists decrease human ureteric peristalsis in in-vitro studies; nifedipine appears to be the most effective drug. Within the ureter, calcium is necessary to develop the action potential and therefore contraction of the ureter. Calcium-channel blockers prevent calcium influx and so would be expected to have an inhibitory effect on ureteric function. There have been conflicting early results on their clinical efficacy in treating acute renal colic. A prospective, double-blind, randomized trial using nifedipine in the acute phase showed that 10–20 mg of oral nifedipine provided significant pain relief in only 23% of patients and had no beneficial effect over placebo after 30 min [18]. Subsequent trials suggested that although nifedipine appears to be inadequate for pain relief in the acute setting, it may be useful, when used regularly, in promoting conservative management of renal colic. A prospective, double-blind, randomized trial comparing avofortan (3.1 vs 15.4 min) and with no side-effects [20]. Acupuncture may work by increasing the levels of endogenous opiates within the cerebrospinal fluid, as drugs able to block morphine also inhibit acupuncture analgesia.

In summary, more research is certainly warranted to determine whether any of these drugs should be used routinely in the conservative management of renal colic. Calcium-channel blockers, especially nifedipine, appear to be the most promising.

### TABLE 3 The effect of nifedipine with or without a steroid on stone passage rates, mean time to stone passage and analgesic use in two reports

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous stone passage, %</td>
<td>87</td>
<td>65</td>
</tr>
<tr>
<td>Time to stone passage, days</td>
<td>11.2</td>
<td>16.4</td>
</tr>
<tr>
<td>Average total diclofenac use, mg</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*8 mg methylprednisolone + 20 mg nifedipine twice daily for 45 days, or + placebo; 130 mg deflazocort (10 days) + 30 mg nifedipine slow-release (28 days) or placebo.

### ALTERNATIVE METHODS OF ANALGESIA

Local active warming of the abdomen and lower back region is an effective analgesic and useful during the emergency transfer to hospital of patients with suspected renal colic. Visual analogue scores were used to compare pain before and after treatment, and between the group receiving warming and those who received no warming. The former patients reported a significant pain decrease, from 83/100 to 36/100, compared with 82/100 to 81/100 in the untreated group [19]. There was also a significant decrease in the anxiety score (79/100 to 31/100) in the treatment group.

Acupuncture is used effectively in China and Taiwan; the analgesic effect occurs much earlier than with their conventional analgesics, avofortan (3.1 vs 15.4 min) and with no side-effects [20]. Acupuncture may work by increasing the levels of endogenous opiates within the cerebrospinal fluid, as drugs able to block morphine also inhibit acupuncture analgesia.

### CONCLUSION

Opiate analgesics and NSAIDs remain the most effective commonly used analgesics for treating renal colic. Because of the side-effect profiles associated with both these groups, alternative methods of treatment are sought. At present, suitable alternative analgesics include tramadol and selective COX II inhibitors. Alternative drugs showing promise include calcium-channel blockers, especially nifedipine, and α-receptor antagonists. Both these groups warrant further attention to determine their value in managing ureteric calculi and the associated pain, and the admissions for intervention (both statistically significant). Unfortunately, because of the use of so many drugs it is difficult to determine the apparent benefit from tamsulosin alone. Polypharmacy also decreases compliance and increases the risk of side-effects, and would not be routine practice in the UK.
possibility of facilitating spontaneous stone passage. Finally, local active warming during the emergency transfer of these patients appears to be an effective method of providing analgesia and anxiolysis before arrival at hospital.

CONFLICT OF INTEREST
None declared.

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Abbreviations: COX, cyclooxygenase; GTN, glycerol trinitrate.
Lymph node metastases in non-muscle invasive bladder cancer are correlated with the number of transurethral resections and tumour upstaging at radical cystectomy

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OBJECTIVE
To identify clinical variables associated with the prevalence of lymph node metastases (LNMs) in patients with non-muscle invasive transitional cell carcinoma (TCC) of the bladder treated with radical cystectomy.

PATIENTS AND METHODS
Of 866 patients treated by radical cystectomy and pelvic lymphadenectomy between 1989 and 2002, 219 had non-muscle invasive TCC of the bladder. A retrospective evaluation of these patients included univariate and multivariate analyses of sex, age, number of transurethral resections of the bladder tumour (TURBTs), interval between first TURBT and cystectomy, adjuvant therapy, maximum histopathological tumour stage and grade at TURBT, and tumour upstaging in the cystectomy specimen.

RESULTS
LNMs were diagnosed in 33 patients (15%). After multivariate analysis modelling, the number of TURBTs and tumour upstaging in the cystectomy specimen were correlated with the prevalence of LNMs at cystectomy. The number of TURBTs increased the prevalence of LNMs from 8% in patients with one TURBT to 24% in those with two to four TURBTs. Tumour upstaging in the cystectomy specimen increased the prevalence of LNMs from 4% to 36%.

CONCLUSION
Inappropriate delay and inadequate staging of high-grade non-muscle invasive TCC of the bladder are to be avoided. The present multivariate analysis showed that the number of TURBTs and tumour upstaging in the cystectomy specimen correlated with an increased prevalence of LNMs.

KEYWORDS
bladder tumour, number of transurethral resections of bladder tumours, tumour upstaging, lymph node metastases

INTRODUCTION
Transurethral resection of bladder tumour (TURBT) is diagnostic and potentially
therapeutic; about two-thirds of tumours are superficial, with no muscle infiltration at first diagnosis, but patients are at risk of tumour recurrence and progression [1,2]. Prognostic factors are: the number of tumours presenting at diagnosis; the interval between first diagnosis and recurrence (<3 months); tumour size (>3 cm); grade of anaplasia of the tumour; invasion of the lamina propria; and presence of carcinoma in situ [3,4]. In tumours with a low risk of progression (pTaG1), adjuvant therapy is primarily intended to reduce recurrences. High-risk tumours (pT1, carcinoma in situ) are generally treated by repeat TURBT and/or adjuvant intravesical instillation therapy to prevent recurrence and progression [4,5]. For high-grade pT1 tumours, recurrence rates after TURBT and intravesical BCG instillation have been reported to be 23–74% [2,5,6]. About 15% of patients who present with non-muscle-invasive TCC of the bladder at TURBT develop invasive tumours; pT1G3 tumours are particularly at risk of progressing, so some authors recommend early cystectomy for these cases [1,7,8]. The probability of lymph node metastases (LNMs) at cystectomy increases with tumour stage, and significantly lowers tumour-specific survival rate [8,9].

As a tertiary referral centre, our patients treated by cystectomy include those operated early for non-muscle invasive bladder cancer, and those treated with delayed cystectomy after several previous therapies. In the present study, we retrospectively evaluated the clinical variables associated with LNMs in patients who underwent radical cystectomy for non-muscle invasive TCC of the bladder.

**PATIENTS AND METHODS**

Of 866 patients who were referred for radical cystectomy and pelvic lymphadenectomy to our institution between 1989 and 2002, 219 (185 men, 34 women, mean age 65.3 years, range 44–83) had non-muscle invasive TCC of the bladder. All patients had at least one therapeutic TURBT before cystectomy. The mean (median, range) number of TURBTs was 2.6 (2, 1–21) (Table 1). Forty-one patients had adjuvant therapies before referral for cystectomy; 37 had adjuvant instillations (BCG, mitomycin, thiotaque), two were treated by adjuvant external irradiation and two received adjuvant systemic chemotherapy (combination methotrexate, vinblastine, doxorubicin and cisplatin). Patients were stratified according to the presence or absence of LNMs at the time of radical cystectomy. The prevalence of LNMs was correlated with: sex, age, number of TURBTs, interval between first TURBT and cystectomy, adjuvant therapy after TURBT, maximum histopathological tumour grade, tumour stage at TURBT, and tumour upstaging in the cystectomy specimen. The number of TURBTs and the interval between the first TURBT and cystectomy were examined both as continuous variables and when categorized according to the median values. Categorized numbers of TURBTs were subdivided according to the distribution of numbers of TURBTs. Standard descriptive statistics, e.g. the mean, quartiles, range frequencies were calculated to describe the study population, the studied clinical variables and the outcome variables. Logistic regression was used to analyse the explanatory value of the examined variables with the prevalence of LNMs, using a forward and a backward stepwise selection, with the likelihood-ratio criterion (inclusion/exclusion criteria: $P \leq 0.05/0.1$, respectively).

For each model, numbers of valid cases are stated, as well as included and excluded variables assessed for the correlation with LNMs. At the beginning of model building, $P$ values of the score test for each of the correlated variables were analysed univariately. In the next step of parameter selection, $P$ values of the score test for excluded variables were calculated. For final model building, odds ratios (OR) of the included variables were calculated, with 95% CI and $P$ values of the likelihood ratio given. All analyses are regarded as explorative and $P$ values given descriptively.

**RESULTS**

Table 1 shows the treatment procedures and tumour grade and stage characteristics of the patients included in the study. Of the tumours graded pTa at TURBT, one was G1 (6%), 14 were G2 (88%) and one was G3 (6%). Of the tumours graded pT1 at TURBT, 45 were G2 (27%) and 123 were G3 (73%). The mean (median, range) interval from first TURBT to cystectomy was 4 (19.6, 1–355) months. There was pathological tumour upstaging in cystectomy specimen in 77 (35%) patients. Of these, 61 (79%) had pT1 tumours at TURBT, seven (9%) pTa, six (8%) pT1 + pTis and three (4%) pTis. Tumour stage was unchanged in 78 patients (36%), but tumour stages were lower in 24 (11%); 40 (18%) had no residual tumour in the cystectomy specimen. Table 2 compares the maximum histopathological tumour stage at TURBT with stage in the cystectomy specimen.

At radical cystectomy, LNMs were found in 33 patients (15%); of these, 24 had pT1G3 tumours at TURBT, five had pT1G2, and one each had pT1 + pTis, pTis, pTaG2 and pTaG3. LNMs were found in seven of 90 patients (8%) with one TURBT, and in 26 of 129 (20%) with at least two TURBTs (25 of 106, 24%, with 2–4 TURBTs); in nine of 77 patients (36%) who presented with higher tumour stages at cystectomy than at TURBT, and in five of 142 patients (4%) with the same or lower tumour stages, or with no residual tumour at cystectomy, in 11 of 33 patients (33%) with adjuvant therapies after TURBT and in 22 of 156 (14%) with no adjuvant therapies; for these groups the median interval between the first TURBT and cystectomy was 28 and 3 months, respectively, and the median number of TURBTs 4 and 2, respectively.

**TABLE 1 Patient characteristics**

<table>
<thead>
<tr>
<th>Variable</th>
<th>N patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of TURBTs</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>90 (41)</td>
</tr>
<tr>
<td>2</td>
<td>51 (23)</td>
</tr>
<tr>
<td>3</td>
<td>33 (15)</td>
</tr>
<tr>
<td>4</td>
<td>22 (10)</td>
</tr>
<tr>
<td>5–21</td>
<td>23 (11)</td>
</tr>
<tr>
<td>Interval between first TURBT and cystectomy</td>
<td></td>
</tr>
<tr>
<td>≤4 months</td>
<td>107 (52)</td>
</tr>
<tr>
<td>&gt;4 months</td>
<td>100 (48)</td>
</tr>
<tr>
<td>Adjuvant therapy after TURBT</td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>186 (85)</td>
</tr>
<tr>
<td>yes</td>
<td>33 (15)</td>
</tr>
<tr>
<td>Maximum tumour grade at TURBT</td>
<td></td>
</tr>
<tr>
<td>G1–2</td>
<td>67 (31)</td>
</tr>
<tr>
<td>G3</td>
<td>152 (69)</td>
</tr>
<tr>
<td>Maximum tumour stage at cystectomy</td>
<td></td>
</tr>
<tr>
<td>pTa</td>
<td>16 (7)</td>
</tr>
<tr>
<td>pTis</td>
<td>15 (7)</td>
</tr>
<tr>
<td>pT1</td>
<td>168 (77)</td>
</tr>
<tr>
<td>pT1 + pTis</td>
<td>20 (9)</td>
</tr>
<tr>
<td>Tumour upstaging at cystectomy</td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>142 (65)</td>
</tr>
<tr>
<td>yes</td>
<td>77 (35)</td>
</tr>
</tbody>
</table>
In 207 patients, statistical analyses were completed for correlation of the selected variables with the prevalence of LNMs. Tumour upstaging at cystectomy (yes vs no, OR 22.3, 95% CI 7.5–65.9) was significantly correlated (P < 0.001) and categorized number of TURBTs (2–4 vs 1, OR 6.9, 95% CI 2.4–20.1; > 4 vs 1, OR 0.6, 95% CI 0.1–5.5, P < 0.001) revealed strong correlations with the prevalence of LNMs on forward selection. Sex, adjuvant therapy after TURBT and categorized interval were not significantly correlated in the last step of the forward parameter selection (P = 0.1018, 0.14 and 0.1359, respectively). All other excluded variables had even larger P values (P > 0.3).

Using the backward selection process, sex (male vs female, OR 2.7, 95% CI 0.8–8.5, P = 0.099) was included additionally in the final model. Tumour upstaging (yes vs no, OR 19.6, 95% CI 6.6–58.1, P < 0.001) and categorized number of resections (2–4 vs 1, OR 7.2, 95% CI 2.6–20.0, category > 4 not included, P < 0.001) remained significant on backward selection. Table 3 gives P values for the univariate score tests of all variables at the beginning of model building and for the variables excluded in the last step of the multivariate analysis.

### DISCUSSION

TURBT is diagnostic and, for non-muscle invasive tumours, is a potentially therapeutic intervention for treating TCC of the bladder. Some tumours are at risk of progression to invasive disease, so many authors recommend adjuvant intravesical therapy to prevent recurrence and progression to higher tumour stages [6,10]. Other authors prefer early cystectomy to improve survival and reduce the risk of early metastases: Stöckle et al. [7] studied 68 patients with superficial bladder cancer who were treated by early cystectomy or repeated TURBT; the 5-year survival was 90% and 62% respectively, and the difference in survival statistically significant. Herr et al. [11] also reported a better long-term survival rate (92% vs 56%) for patients treated by early cystectomy (52 vs >2 years after initial BCG therapy) for high-risk superficial bladder carcinoma.

The presence of LNMs at the time of cystectomy lowers survival rates significantly [8,9,12,13]. Frazier et al. [9] reported that the median tumour-specific survival was 1 year for patients with LNMs at cystectomy and 9.3 years for patients with no LNMs. Nodal metastases were found in four of 148 patients (3%) with pT1 tumours. Amling et al. [12] reported that 5.9% of patients with pT1 tumours had LNMs. In the present series, 33 of 219 (15%) patients with non-muscle invasive bladder tumours who underwent radical cystectomy had LNMs.

The interval between the first resection and cystectomy might be prolonged by repeated TURBTs, adjuvant therapies, or late recurrence after primary TURBT with no intercurrent recurrences or adjuvant therapies. Deciding on conservative or radical treatment might be based on the existence of residual tumour after TURBT, and/or understaging at the first TURBT. Some authors perform a second TURBT to exclude or remove residual tumour and to minimize the risk of staging errors at TURBT. Herr [14] investigated the role of a repeat TURBT, 114 of 150 patients (76%) had residual tumour on repeat TURBT, and 28 (29%) were upstaged to invasive tumour disease. In a study by Brauers et al. [10], a second TURBT within 2–6 weeks after TURBT was used for pT1 tumours, revealing residual tumour in 27 of 42 (64%) of patients. Tumour upstaging and change of the treatment strategy was reported in 10 of 42 patients (24%). The rate of organ preservation was 100% in patients with no residual tumour at the second TURBT, but the tumour recurrence rate was 33% in this group. Dutta et al. [1] reported clinical understaging by TURBT in 31 of 78 patients (40%) after cystectomy for superficial bladder cancer, and 29 (37%) were refractory to intravesical treatment. In other studies, tumour understaging at TURBT was 30–40% [15–17]. Clinically understaged patients have a poorer survival rate; Amling et al. [12] reported that patients with pT1 tumours at TURBT which remained pT1 in the cystectomy specimen have a median survival of 12.1 years, compared to 5.7 years for patients with histopathological tumour upstaging. In another study, median survival for patients with superficial bladder tumours was...
10.2 years, compared with 6.9 years for those with understaged tumours at TURBT [17].

In the present series, the rate of tumour upstaging was 35%, which is similar to other reported values [12,17]. Tumour upstaging increased the prevalence of LNMs from 4% to 36%. Possible causes for the 35% rate of tumour upstaging might be inadequate resection with histopathological understaging (e.g. because of lack of detrusor in the specimen), residual tumour after TURBT, or tumour progression until radical cystectomy.

A statistically significant effect of increasing the disease-free interval after TURBT was reported for intravesical treatment with BCG or chemotherapeutic agents, but positive effects on development of metastases and tumour-related deaths were not apparent [18]. Intravesical BCG instillation therapy is the recommended treatment for tumours with a high risk for progression (T1G3, carcinoma in situ) [5,19]. Sylvester et al. [19] meta-analysed 24 trials with information of tumour progression on 4863 patients with superficial bladder tumours. Tumour progression was seen in 9.8% of patients after TURBT plus BCG, compared to 13.8% of the control group. The treatment effect did not influence tumour-specific survival. Brake et al. [8] treated 44 patients who had pT1G1-3 tumours with BCG after TURBT; 36 (82%) were tumour-free after one or two cycles at 3 years of follow-up. The overall recurrence rate was 27% and the tumour progression rate 16%. The risk of tumour progression after repeated BCG courses increases with increasing numbers of failures [20].

In the present series, the prevalence of LNMs was significantly correlated with the interval between the first TURBT and cystectomy, and with the history of adjuvant therapies. The prevalence of LNMs was increased from 8% to 22% for intervals >4 months, and from 14% to 33% for a history of adjuvant therapy. However, neither variable was recognized as a correlating factor in the multivariate analysis model.

In the present study, 89.5% of the patients had either one TURBT (41%), or 2–4 TURBTs (48%). In the multivariate analysis the number of TURBTs (1 vs 2–4) was significantly correlated with the prevalence of LNMs. Possible causes of an increased risk of LNMs after multiple TURBTs may be lymphatic spread of cells during TURBT or delay of radical surgery with tumour progression.

In conclusion, an inappropriate delay before cystectomy and inadequate staging of high-grade non-muscle invasive ICC of the bladder is to be avoided. In the present series, tumour upstaging in cystectomy specimens and the number of TURBTs were correlated with the prevalence of LNMs in a multivariate analysis.

### CONFLICT OF INTEREST

None declared.

### REFERENCES

LYMPH NODE METASTASES IN NON-MUSCLE INVASIVE BLADDER CANCER


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e-mail: ChristophWs@AOL.com

Abbreviations: TURBT, transurethral resection of bladder tumour; LNMs, lymph node metastases; OR, odds ratio.
Urinary acetonitrile concentrations correlate with recent smoking behaviour

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Accepted for publication 20 September 2004

OBJECTIVES
To assess the concentration of acetonitrile (a saturated aliphatic nitrile) in the urine of habitual cigarette smokers and non-smokers, as exposure to smoke can be measured by monitoring ambient air or by in vivo tests, but acetonitrile measured in exhaled breath is reportedly a quantitative marker of recent smoking behaviour.

SUBJECTS AND METHODS
The study included 101 volunteers (57 men and 44 women, mean age 49 years). An absence of urinary tract infection on urine analysis or clinical history was mandatory. The subjects were classified into five groups, i.e. a control group of non-smokers and four groups according to the number of cigarettes smoked daily. Urine samples were stored at 8 °C until acetonitrile was measured, within 24 h of collection, using proton-transfer reaction mass spectrometry (PTR-MS). Each measurement was repeated at least 10 times, and the mean used for statistical analysis.

RESULTS
The mean (SD) acetonitrile level in the urine of 46 non-smokers was 3.74 (1.78) parts per billion volatile (ppbv). The concentration of acetonitrile increased with the number of cigarettes smoked daily, the highest concentration being in the subgroup of 13 very heavy smokers (>30 cigarettes/day) with means up to 28.04 (5.38) ppbv.

CONCLUSION
PTR-MS is a quick, noninvasive online method for determining urinary acetonitrile levels, a marker for recent active and passive smoking behaviour, and thus for checking compliance. As smoking has been shown to affect the genesis of bladder cancer, further studies are required to determine the association of acetonitrile with bladder cancer.

KEYWORDS
markers, urine, smoking, nicotine, acetonitrile, bladder cancer, carcinogen

INTRODUCTION
It is estimated that worldwide, 1.2 billion people smoke an average of 14 cigarettes each per day. In the USA an estimated 47 million adults are currently cigarette smokers; ~80% of adult tobacco users initiate use before 18 years of age [1,2]. According to the Centers for Disease Control and Prevention (1999) national data on USA high-school students, more than a third (35%) were current smokers, and a quarter smoked a whole cigarette before 13 years old. The age at which smoking begins has been shown not only to influence the total number of years of smoking, but even more the number of cigarettes smoked per day in adulthood [3,4], and the likelihood of quitting [5,6]. According to Everett et al. [7] a lower age when starting smoking is associated with smoking more cigarettes per day than starting when older.

In the last 20 years, cigarette smoking has been shown to be strongly associated with the development of bladder cancer [8–10]. Tobacco-smoking is responsible for 30–40% of bladder cancer in developed countries [11]. The duration of cigarette smoking has a direct relationship with the relative risk of developing bladder cancer [12–14].

Exposure to tobacco smoke may, in principle, be evaluated using ambient-air monitoring or by assays involving in vivo biomarkers of smoking. Recently, acetonitrile was reported to be a possible marker of recent smoking behaviour in human exhaled breath [15,16]. Proton transfer reaction mass spectrometry (PTR-MS) has been established as a valid tool for measuring ambient air [17] and exhaled breath in various settings [18,19].

The aim of the present study was to assess urinary acetonitrile levels in smokers and non-smokers, using PTR-MS; the null hypothesis was that mean acetonitrile levels would not differ significantly among groups.

SUBJECTS AND METHODS
The study included 101 volunteers (patients and staff, 57 men and 44 women) enrolled at the department of urology (mean age 49 years). None of the enrolled subjects had any clinical medical history of renal or cardiopulmonary disease; in all volunteers the blood creatinine values were within normal ranges. Informed consent was obtained from each participant. Volunteers were asked to donate a urine sample before noon into a glass tube. Samples were stored at 8 °C for at most 24 h before acetonitrile was measured. All participants completed a questionnaire about cigarette smoking habits, time elapsed since their last cigarette, and a detailed clinical history. Cigar or pipe smokers were excluded from the study. To exclude a possible bacterial UTI, all samples were evaluated using a urinary dipstick (Combur Stix, Roche Diagnostics, Germany). Based on the number of cigarettes smoked daily, subjects were divided into five groups: group 0 (control), 46...
**RESULTS**

In group 0 the mean acetonitrile level was 3.74 (1.78) ppbv; the concentration then increased proportionally with the number of cigarettes smoked daily (Fig. 1), with the highest concentration in group 4, at 28.0 (5.38) ppbv. All groups showed a statistically significant dose-response correlation. Because the t-test was two-tailed, every group comparison was significant. The two-tailed correlation was highly significant, with a correlation of 0.911, at $P < 0.01$ (Fig. 1). Furthermore, there was dose-dependent increase in urinary acetonitrile concentration, with a linear regression coefficient of 5.783, which was even more significant ($P < 0.001$). In both analyses, acetonitrile concentration in the urine was the dependent variable.

To exclude the influence of time from sample collection to measurement on the acetonitrile level, five separate urine samples were measured at 4, 12, 24 and 36 h after the first analysis (Fig. 2), showing no notable decrease of acetonitrile over time. Only after 36 h was there a slight decline (21.8% of the initial value) in the acetonitrile concentration. The variables of gender and age of the participants showed no statistically significant correlation with acetonitrile level.

**DISCUSSION**

The main objective of the present study was to determine possible differences in urinary acetonitrile levels between smokers and non-smokers; there was a correlation between acetonitrile concentrations and recent smoking behaviour.

PTR-MS has been reported to reliably allow for both single and real-time measurements of volatile organic compounds in exhaled air [18,19]. A dose-dependent correlation between cigarette consumption and levels of acetonitrile in exhaled air was recently reported [18]. Acetonitrile seems to be a useful variable for monitoring cigarette consumption for two reasons. First, according to Lindinger et al. [16], non-smokers have very low concentrations of acetonitrile in their breath (5–10 ppbv), whereas smokers have 30–100 ppbv. Second, it takes a week for acetonitrile concentrations to return to normal after cessation of smoking. However, no investigations have been carried out so far examining possible correlations between urinary acetonitrile and smoking behaviour.

The present results showed a statistically significant dose-response curve to the number of cigarettes smoked daily.

A standardized 'second puff' of cigarette smoke contains 0.31 mg acetonitrile, and a smoker, depending on his or her smoke-inhaling habit, may absorb 74–91% of the...
Evidence for the carcinogenic property of acetonitrile [20,21]. All of the present smokers were habitually deep inhalers who used no filters, so that according to Dalhamn et al. [20] they can be expected to absorb ~91% of the acetonitrile. The influence of the brand of tobacco was not evaluated in this study.

Despite a genetic susceptibility, bladder cancer appears to be mostly the result of exogenous anthropogenic risk factors. Different lifestyles and environmental factors contribute to the enhanced cancer risk worldwide. Cigarette smoking has been shown to be strongly associated with the development of bladder cancer [9,10,22]; the relative risk has been calculated to be twice [23] to 10 times depending on the accumulated dose [24]. Smoking is estimated to be responsible for ~47% of bladder cancer deaths among men and 37% among women in the USA [25]. In view of the widespread consumption of cigarettes and the long-term effects of smoking over decades, the role of continuously inhaled substances is particularly significant.

The mechanism of cigarette-induced bladder cancer is most likely related to numerous chemicals in cigarette smoke. There are >4000 substances identified in the mainstream smoke, of which >40 are known or suspected to cause cancer in humans and animals, and many of which are toxic or strong irritants. Since the first publication from Ludwig Rehn in 1895 about the increased incidence of bladder cancer in industry workers, considerable evidence has accumulated for the involvement of known carcinogenic substances, e.g., aromatic amines, in bladder cancer induction.

Based on the present results we suggest that the urothelium of the bladder will be affected in a dose-dependent fashion by a recurrent and prolonged period of exposure to low acetonitrile concentration. As the human urinary bladder is a reservoir, the bladder urothelium is in contact for a longer with excreted compounds, and the bladder is potentially exposed to acetonitrile to a higher degree than the kidney or other urothelial cells. Indeed, of all the cancers in the urinary tract, nearly 92.5% are found in the urinary bladder. Furthermore, the endothelial surface of the urinary bladder comprises ~93% of that of the entire urinary tract.

There are no animal experiments providing evidence for the carcinogenic property of acetonitrile, and thus it was classified as a 'category D' substance according to the current Risk Assessment Guidelines. However, these experiments (which implies no proven human carcinogenicity) investigated the influence of acetonitrile on several organs such as the kidney, liver, fore stomach etc. No study investigated the carcinogenic influence of acetonitrile on the urinary bladder. However, we suggest that it is the bladder which is subjected to prolonged and intermittent exposure to this compound, so that it cannot be excluded that acetonitrile is important in the genesis of bladder cancer. For example, in experiments with Carworth Farms-Wistar rats, even subchronic exposure to acetonitrile provoked a tubular swelling in the kidneys in eight out of 27 animals (P = 0.05) [26]. Analogous results, with cloudy swelling of the proximal and convoluted tubules of the kidney, were obtained with rhesus monkeys and male dogs. This argues for the direct influence of prolonged exposure to acetonitrile on the urothelium. Finally, there are no data on the implications of prolonged acetonitrile exposure of the human bladder in such low concentrations, as measured here for the first time (ppbv).

In addition to acetonitrile excretion after active cigarette smoking, the role of passive inhalation of cigarette smoke should be considered. In passive smokers the mean acetonitrile concentration nearly reached values in the subpopulation of moderate smokers (mean 8.2 vs 12.95 ppbv in group 2, data not shown). Although the classification into passive smokers is based on a questionnaire with no exact exposure stratification, it seems that environmental tobacco exposure determines the measured acetonitrile concentrations in the control group. This was not surprising, as Dalhamn et al. [27] showed that 74% of inhaled acetonitrile was adsorbed when smoke was held in the mouth for 2 s (and not inhaled), whereas 91% was absorbed when the smoke was inhaled.

PTR-MS for measuring acetonitrile in urine samples is a simple, noninvasive and cost-effective approach that can detect the cigarette-smoking habits of patients. Such measurements may have a role in the future in health-risk assessment by insurance companies and in public health policies. Being noninvasive, the method can be used routinely, analogous to exhaled-breath testing [19,28]. In addition to assessing smoking status, PTR-MS can be used to monitor dyslipidaemia therapy in exhaled air [18]. It is therefore conceivable to jointly investigate two high-risk factors by one simple method.

Finally, there are some limitations of the present study; the possibility of substances interfering with the specific molecule investigated must be considered. The presence of a baseline value of mass 42 even in non-smokers in whom no acetonitrile was found on gas chromatography [15] suggests a cautious interpretation of the present results. The detection of a very low urinary acetonitrile concentration in the first group of non-smokers could imply a ubiquitous, hidden presence of acetonitrile.

In conclusion, this is the first study in which PTR-MS was used to detect urinary acetonitrile in healthy cigarette smokers, with acetonitrile showing a significant dose-dependence. Furthermore, the study showed for the first time the feasibility of acetonitrile detection in a particularly low range (ppb) by PRT-MS. Analysis of urinary acetonitrile may serve as a quick and noninvasive marker to determine recent active and passive smoking behaviour, and to check compliance. In lifelong smokers the urothelium of the bladder is exposed repeatedly and continuously to low acetonitrile concentrations in a dose-dependent fashion, and this exposure might constitute a risk for bladder cancer. Ongoing investigations in our department are evaluating the usefulness of incorporating acetonitrile measurements in the assessment of bladder cancer screening protocols.

CONFLICT OF INTEREST

None declared.

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Abbreviations: PTR-MS, proton transfer reaction mass spectrometry; ppbv, parts per billion volatile.
The pT1a and pT1b category subdivision in renal cell carcinoma: is it reflected by differences in tumour biology?

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OBJECTIVE
To assess systematically the possible differences in pathology between pT1a and pT1b renal cell carcinomas (RCCs), as the sixth edition of the Tumour-Nodes-Metastasis (TNM) system implemented a subdivision of category pT1 into pT1a (<4 cm) and pT1b (4–7 cm), based on clinical outcome analysis and the approach to therapy.

RESULTS
After 2 years of follow-up, none of the 66 patients with pT1a and three of the 29 with pT1b tumours developed progressive disease. The tumour was grade 3 in four (6%) pT1a and 11 (38%) pT1b RCCs. Immunohistochemically, pT1a RCCs were characterized by strong expression of p27 (79%), bcl-2 (67%), MUC1 (87%), insulin-like growth factor (IGF)-1 (71%) and CD10 (88%), as well as moderate expression of IGF-I receptor (43%) and low expression of epidermal growth factor receptor (EGFR, 20%). During progression to category pT1b, expression of p27 significantly decreased (54%) and EGFR expression increased (38%). Moreover, membranous staining patterns of MUC1 and CD10 changed from apical to circumferential in clear cell RCCs. p53 (pT1a 23%, pT1b 28%), E-cadherin (10% and 17%), MIB-1 (1.2% and 1.5%) and Skp2 (2% and none) expression seemed to be of minor importance.

CONCLUSION
This is the first study to show that the subdivision of category pT1 implemented in the latest issue of the TNM system is reflected by differences in conventional histopathology and expression of biomarkers.

KEYWORDS
renal cell carcinoma, TNM, tumour category, pathology, immunohistochemistry, tissue microarray

INTRODUCTION
The TNM staging system published by the Union Internationale Contre le Cancer (UICC) represents an international collaborative effort to standardize the assessment of the extent of cancer spread at the time of diagnosis. In the 1997 (Fifth) edition the tumour size used as a threshold between categories pT1 and pT2 for RCC was changed from 2.5 to 7 cm. Since then, several studies investigating the clinicopathological data of patients with category pT1 RCCs detected significant differences in the patients’ outcome at consistent threshold tumour diameters of 4–5.5 cm [1–5]. These observations and different strategies of treatment planning dependent on tumour size [e.g. selecting patients for partial nephrectomy] led to the suggestion of a subdivision of category pT1 into pT1a (<4 cm) and pT1b (4–7 cm) by Workgroup no. 3 of the UICC and the American Joint Committee on Cancer [6], which was finally implemented in the recent modification of the TNM staging system from 2002 [7]. However, this latest modification was based on clinical outcome analysis and approach to therapy only, while data on associations with histopathological variables are currently lacking.

Therefore, we systematically analysed 95 pT1 RCCs to identify possible differences in both conventional histopathology and expression of biomarkers between pT1a and pT1b tumours, according to the recent update of the TNM system [7]. Proteins analysed included the proliferation marker Ki-67 (MIB-1), those involved in the regulation of cell-cycle progression and apoptosis (p53, bcl-2, p27, Skp2) or cell adhesion (E-cadherin, MUC1), IGF-I and its receptor (IGF-IR), epidermal growth factor receptor (EGFR) and the membrane-associated neutral endopeptidase CD10, known to be involved in signalling processes.

PATIENTS AND METHODS
In all, 95 paraffin-wax embedded specimens from 94 consecutive patients (60 men and 34 women, ratio 1.8 : 1, mean age at surgery 62 years, range 28–85) with pT1 RCCs operated between October 1997 and October 2001 were chosen for analysis. All specimens were re-evaluated for pT category, tumour grade and histological subtype, according to the WHO guidelines [8], by two pathologists (C.L. and M.R.). Category pT1a was present in 66 of 95 (69%) tumours (mean 2.7 cm, range 1–4) and pT1b in 29 (31%) (mean 5.2 cm, range 4.1–6.5). Tumour grade was assessed using the Fuhrman grading system [9].

For the immunohistochemical evaluation, a tissue microarray technique was used, as described previously [10]. Because of the well known histological heterogeneity of RCCs at least three cylindrical core biopsies (0.6 mm in diameter) were taken from different sites of
each tumour. Briefly, 4 µm sections were deparaffinized, treated with 1% H2O2, subjected to antigen retrieval and subsequently incubated for 30 min with monoclonal primary antibodies (MB-1 polyclonal) applying an automated immunostainer (Universal Staining System, DakoCytomation, Glostrup, Denmark). Details on antigen retrieval, primary antibodies and positive controls are listed in Table 1. Binding of primary antibodies was assessed by the Dako LSAB® 2 System and the Dako EnVision™ System detection kits, respectively. Negative controls included omission of the primary antibodies and incubation with Dako ChemMate™ Antibody Diluent (Code No. S 2022).

In general, immunoreactivity was independently assessed semi-quantitatively by two pathologists (C.L. and M.R.) who were unaware of the clinicopathological data. Discrepancies were resolved by simultaneous re-examination of the slides by both investigators, using a double-headed microscope. 'High' expression was defined as immunoreactivity of more than half the cancer cells. Ki-67 (MB-1) immunoreactivity was evaluated using a semiautomatic image analyser, consisting of an Eclipse E600 microscope (Nikon, Tokyo, Japan) with 0.40/20 Plan achromat objective used for measurements, a 3CCD video camera DXC-930P (Sony, Tokyo, Japan), an IntriguePro image frame grabber (Integral Tech., USA) and a personal computer. The system was controlled by Optimas 6.5 image analysis software (Media Cybernetics Inc., USA). Cases were considered sufficient for evaluation when at least 500 tumour cells were present in the core biopsies.

Tumours of pT1a and pT1b were compared for possible differences in immunoreactivity using Fisher's exact test or the Mann–Whitney U-test. Disease-free survival of patients with pT1a and pT1b tumours was evaluated using the Kaplan–Meier method and compared by the log-rank test.

**RESULTS**

In the pT1a group, histological subtypes were clear cell in 50 of 66 (76%), papillary in seven (11%) and chromophobe in nine (14%) RCCs; the pT1b group consisted of 21 of 29 (72%) clear cell, four (14%) papillary and four (14%) chromophobe RCCs. In pT1a and pT1b tumours respectively the grade was 1 in 16 (24%) and two (7%) (P = 0.05), grade 2 in 46 (70%) and 16 (55%) (P = 0.2) and grade 3 in four (6%) and 11 (38%) (P < 0.001). For the clear cell subtype only, the results were similar, with grade 1 in 15 of 50 (30%) and two of 21 (10%) (P = 0.08), grade 2 in 32 (64%) and 12 (57%) (P = 0.6), and grade 3 in three (6%) and seven (33%) (P = 0.006), respectively.

The median (range) immunoreactivity for Ki67 (MB-1) was 1.4 (0.1–8.7)%, with pT1a and pT1b tumours showing similar staining results (1.2% and 1.5%; P = 0.43; Mann–Whitney U-test). pT1a RCCs showed strong expression of p27, bcl-2, MUC1, IGF-1 and CD10, moderate expression of IGF-IR and weak expression of p53, EGFR, E-cadherin and Skp2 (Table 2).

The pT1b tumours expressed p27 significantly less often, while EGFR immunoreactivity increased (Table 2), for the clear cell subtype only the results were comparable. For the other biomarkers pT1b RCCs gave staining results comparable with pT1a tumours (Table 2). Results were similar when pT1a and pT1b clear cell RCCs were analysed separately. Staining for Skp2 yielded negative results.

For clear cell RCCs only, the patterns of immunoreactivity differed for MUC1 and CD10; overall, there was predominantly apical membranous staining in 54 of 58 (93%) tumours for MUC1 and in 26 of 59 (44%) for CD10, the remaining tumours giving a predominantly circumferential membranous immunoreactivity. However, the latter was seen in one of 41 (2%) pT1a and three of 17 pT1b RCCs (P = 0.07) for MUC1 and in 19 (46%) pT1a and 14 of 18 pT1b (P = 0.045) for CD10.

After a mean and median follow-up of 27 months, three of the 94 (3%) patients developed metastatic disease. All three cases of tumour progression were among the 29 patients with poorly differentiated (G3) pT1b tumours, corresponding to a progression rate of 10%, whereas none of the 65 patients with pT1a RCCs developed metastatic disease. All three cases of tumour progression were among the 29 patients with poorly differentiated (G3) pT1b tumours, corresponding to a progression rate of 10%, whereas none of the 65 patients with pT1a RCCs developed metastatic disease.

**DISCUSSION**

In renal cancer, tumour stage is the most important variable for prognosis and survival after surgery, and is determined by tumour size and venous involvement. The recent update of the TNM system [7] implemented a subdivision of category pT1 based on clinical outcome analysis and the approach to therapy. To the best of our knowledge, the present study is the first to investigate whether this subdivision is reflected by differences in pathology. All the patients in the series who developed metastatic disease had pT1b tumours. This is in accordance with

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Specificity/clone</th>
<th>Dilution</th>
<th>Source</th>
<th>Retrieval*</th>
<th>Positive control</th>
</tr>
</thead>
<tbody>
<tr>
<td>MB-1</td>
<td>Ki-67</td>
<td>1 : 200</td>
<td>Dako</td>
<td>Citrate</td>
<td>Lymph node</td>
</tr>
<tr>
<td>P27</td>
<td>1B4</td>
<td>1 : 20</td>
<td>Novocastra</td>
<td>Citrate</td>
<td>Lymph node</td>
</tr>
<tr>
<td>Skp2</td>
<td>SKP2</td>
<td>1 : 10</td>
<td>Zymed</td>
<td>Citrate</td>
<td>Lymph node</td>
</tr>
<tr>
<td>P53</td>
<td>DQ-7</td>
<td>1 : 100</td>
<td>Dako</td>
<td>Citrate</td>
<td>Colon cancer</td>
</tr>
<tr>
<td>E-cadherin</td>
<td>4A2C7</td>
<td>–</td>
<td>Zymed</td>
<td>HIER</td>
<td>Breast</td>
</tr>
<tr>
<td>MUC1</td>
<td>Ma695</td>
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<td>Novocastra</td>
<td>HIER</td>
<td>Breast</td>
</tr>
<tr>
<td>CD10</td>
<td>56C6</td>
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</tr>
<tr>
<td>IGF-1</td>
<td>I-5C9</td>
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<td>Linaris</td>
<td>Trypsin</td>
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</tr>
<tr>
<td>IGF-IR</td>
<td>24–31</td>
<td>1 : 50</td>
<td>Neomarkers</td>
<td>EDTA</td>
<td>Colon cancer</td>
</tr>
<tr>
<td>EGFR</td>
<td>H11</td>
<td>–</td>
<td>Dako</td>
<td>Protease</td>
<td>Skin</td>
</tr>
</tbody>
</table>

*Citrate, 0.01 mol/L sodium citrate buffer pH 6.0, 30 min 160 W (microwave); HIER, epitope retrieval solution (Dako, code no. K 5205), 40 min 98 °C; HIER, target retrieval solution (Dako, code no. S 1699), 20 min 750 W (microwave); Trypsin, 1% trypsin (Sigma-Aldrich, Steinheim, Germany), 20 min room temperature; EDTA, EDTA buffer pH 8.0, 30 min 160 W (microwave); Protease, protease K in Tris-HCl buffer (following Dako EGFR pharmDx™ kit).

pT1a AND pT1b RCC
the results of Fergany et al. [3], who reported metastatic disease in six of 21 (29%) pT1b and one of 43 (2%) pT1a tumours. The higher progression rate in that study compared to the present data is probably related to the longer mean follow-up of 104 months (27 months in the present study).

There was a significant difference in tumours grade between the categories in the present series, but this was not reflected by a difference in tumour cell proliferation, as the antibody MIB-1 directed against the Ki-67 antigen, a nuclear cell proliferation-associate protein, gave similar staining results in both groups. Recently, Cheville et al. [11] reported a correlation between MIB-1 immunoreactivity in cancer tissue has been associated with a poor prognosis [13]. To date, Skp2 expression has not been investigated in RCCs; however, the present results suggest that Skp2 expression is of little relevance, at least in early disease stages. p53 is a well known tumour-suppressor gene; its overexpression is significantly associated with both tumour cell proliferation and prognosis in RCCs [14,15]. In the present series the low p53 expression does not suggest a relevant role of p53 in early-stage RCCs. The proto-oncogene bcl-2 encodes an intracellular membrane-associated protein that protects cells from apoptosis. In the present series, bcl-2 immunoreactivity was nearly identical in both subcategories, a result in contrast to that of Lipponen et al. [16], who noted a significant association between the pT1 subcategories. MUC1 is a transmembrane glycoprotein which is known to interfere with both cell-cell and cell-matrix adhesions; clear cell pT1b RCCs tended to lose polarity and switch from purely apical to circumferential membranous immunoreactivity, which we recently showed is associated with an unfavourable prognosis in a large consecutive series of patients with RCC [18].

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Positive, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High expression</strong></td>
<td><strong>pT1</strong></td>
</tr>
<tr>
<td>P27</td>
<td>51/66 (77)</td>
</tr>
<tr>
<td>40/47 (85)</td>
<td>32/55 (58)</td>
</tr>
<tr>
<td>Skp2</td>
<td>1/86 (1)</td>
</tr>
<tr>
<td>0/86</td>
<td>0/58</td>
</tr>
<tr>
<td>P53</td>
<td>22/91 (24)</td>
</tr>
<tr>
<td>0/91</td>
<td>0/62</td>
</tr>
<tr>
<td>BCL-2</td>
<td>57/90 (63)</td>
</tr>
<tr>
<td>28/31 (90)</td>
<td>22/61 (36)</td>
</tr>
<tr>
<td>E-cadherin</td>
<td>11/88 (13)</td>
</tr>
<tr>
<td>8/88 (9)</td>
<td>4/59 (7)</td>
</tr>
<tr>
<td>MUC1</td>
<td>77/90 (85)</td>
</tr>
<tr>
<td>53/90 (59)</td>
<td>39/61 (64)</td>
</tr>
<tr>
<td>CD10</td>
<td>77/87 (89)</td>
</tr>
<tr>
<td>60/87 (69)</td>
<td>41/61 (69)</td>
</tr>
<tr>
<td>IGF-I</td>
<td>64/91 (70)</td>
</tr>
<tr>
<td>21/91 (23)</td>
<td>16/62 (26)</td>
</tr>
<tr>
<td>IGF-IR</td>
<td>37/85 (44)</td>
</tr>
<tr>
<td>17/85 (20)</td>
<td>13/58 (22)</td>
</tr>
<tr>
<td>EGFR</td>
<td>23/89 (26)</td>
</tr>
<tr>
<td>11/89 (12)</td>
<td>5/60 (8)</td>
</tr>
</tbody>
</table>

**TABLE 2**

Differences of immunoreactivity between pT1a and pT1b RCCs for different biomarkers, and for the clear cell subtype only

For proteins involved in cell adhesion, we investigated the expression of E-cadherin, a transmembrane glycoprotein which functions as a calcium-dependent homotypic adhesion molecule, and is expressed by most epithelia [17]. E-cadherin expression was generally weak and we were unable to detect a significant difference in immunoreactivity between the pT1 subcategories. MUC1 is a transmembrane glycoprotein which is known to interfere with both cell-cell and cell-matrix adhesions; clear cell pT1b RCCs tended to lose polarity and switch from purely apical to circumferential membranous immunoreactivity, which we recently showed is associated with an unfavourable prognosis in a large consecutive series of patients with RCC [18].
The IGF family of ligands (IGF-I, IGF-II), receptors (IGF-IR, IGF-IIR) and binding proteins (IGFBP1-6) represents an important growth factor system, including mitogenic and anti-apoptotic effects. In RCCs, the presence of IGF-IR was recently investigated [19], but no data on the expression of its ligands are currently lacking. The detection of both receptor (IGF-IR) and ligand (IGF-I) expression in the present series provides evidence for the existence of an auto- or paracrine loop of tumour cell stimulation in RCC, which is already developed in early tumour categories.

EGFR belongs to the ErbB family of four closely related cell membrane receptors: EGFR (HER1, ErbB1), HER2 (ErbB2), HER3 (ErbB3), and HER4 (ErbB4). These receptors are transmembrane glycoproteins with an extracellular ligand-binding domain and an intracellular domain with tyrosine kinase activity for signal transduction. EGFR activation leads to cell-cycle progression, inhibition of apoptosis, possible promotion of invasion/metastasis and other cellular activities. Members of the ErbB family are overexpressed in a variety of cancers, and an increase in immunoreactivity has been associated with reduced survival [20]. In RCCs, increased EGFR expression seems to be common, and has been associated with increased tumour cell proliferation and poor prognosis [21,22]. The present results indicate that overexpression of EGFR is an early event in RCCs and there was a strong trend towards an association between increased EGFR expression and increasing tumour category.

In the normal kidney, CD10 is expressed on the brush border of proximal tubules and glomerular epithelium. In the present series, CD10 was expressed in most pT1a and pT1b RCCs, which agrees with previous findings [20]. Comparable to MUC1, there was a significant change in membranous staining pattern, from purely apical to circumferential, in clear cell RCCs during tumour progression, which may reflect defects in processing pathways associated with tumour cell de-differentiation [18].

In conclusion, the present study is the first to show that the subdivision of pT1 RCCs implemented in the recent modification of the TNM staging system is reflected by differences in conventional histopathology and expression of biomarkers.

ACKNOWLEDGEMENTS
The authors are grateful to Prof Dr C. Wittekind, University of Leipzig, Germany, for reviewing the manuscript. PD Dr R.v. Wasielewski, Medical School Hanover, Germany, kindly supplied the Skp2 stain, and Prof Dr J. Rüsselhoff, Klinikum Kassel, Germany, the IGF-I stain. Mrs Gogg-Kamerer, Mrs M. Lindbauer, Mrs A. Sommersacher, Mr M. Al-Effah and Mr R. Christof are acknowledged for excellent technical assistance.

CONFICT OF INTEREST
None declared.

REFERENCES


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Abbreviations: UICC, Internationale Contre le Cancer; EGFR, epidermal growth factor receptor.
Kit (CD117) immunoreactivity is rare in renal cell and upper urinary tract transitional cell carcinomas

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OBJECTIVE
To investigate the presence of Kit (CD117), a transmembrane tyrosine-kinase receptor, in primary and metastatic renal cell carcinomas (RCCs) and upper urinary tract transitional cell carcinomas (TCCs).

MATERIALS AND METHODS
In human neoplasia, overexpression of Kit has been related to cell proliferation, differentiation, adhesion and control of apoptosis. If present, Kit may provide a suitable target for tumour therapy. Formalin-fixed and paraffin-embedded specimens of 180 primary and 58 metastatic RCCs and 54 upper urinary tract TCCs were immunostained for Kit (CD117) using a tissue microarray technique.

RESULTS
In RCCs, immunoreactivity for CD117 was detected in only two of 23 (9%) chromophobe tumours, whereas all 137 conventional and 20 papillary subtypes, and metastatic RCC tissues, lacked CD117 immunoreactivity. In TCCs, CD117 expression of <10% cancer cells was found in two of 53 (4%) cases. Stromal mast cells served as a positive control and showed specific immunostaining.

CONCLUSION
Kit immunoreactivity is infrequent in both RCCs and upper urinary tract TCCs. Thus, routine screening of tumour tissues for Kit by immunohistochemistry appears to be cost-ineffective and cannot be recommended. Moreover, the lack of substantial Kit immunoreactivity in both primary and metastatic carcinomas does not provide a rationale to investigate imatinib mesylate therapy in clinical trials including patients with advanced disease.

KEYWORDS
renal cell carcinoma, transitional cell carcinoma, Kit, CD117, immunohistochemistry, tissue microarray

INTRODUCTION
RCCs and TCCs of the upper urinary tract account for 2–3% of new cancer cases each year in the USA [1]; surgery is the treatment of choice. In patients with metastatic disease, immunotherapy (for RCCs) and chemotherapy (for TCCs) are used frequently [2,3], but the prognosis is usually unfavourable, indicating the need for more effective treatment strategies.

The proto-oncogene c-kit encodes a transmembrane tyrosine-kinase receptor (Kit, CD117) that is structurally related to the platelet-derived growth factor (PDGFR)/ colony-stimulating factor-1 subfamily [4]. Stem cell factor (SCF), also known as mast cell growth factor or steel factor, has been identified as the natural ligand of Kit, and Kit protein kinase activity. It is effective for treating chronic myelogenous leukaemias [12] and unrectactable and/or metastatic GISTs [13], raising the hope that other malignancies with Kit overexpression could be treated similarly. The present study was designed to investigate the expression of Kit in many of both primary and metastatic RCCs, and upper urinary tract TCCs, to evaluate the basis for a possible new therapeutic option for patients with advanced disease.

MATERIALS AND METHODS
Formalin-fixed and paraffin-embedded specimens of 180 primary and 58 metastatic RCCs, and 53 primary upper urinary tract TCCs, from consecutive patients operated on at our institution between January 1988 and August 2002, were chosen for analysis. The clinicopathological data are summarized in Table 1. All specimens were re-evaluated by two pathologists (C.L. and M.R.); pT stages were adjusted according to the International Union Against Cancer 2002 issue of the TNM system [15]; grading of TCCs was evaluated according to the WHO guidelines [16], and RCCs were graded according to the more accepted Fuhrman grading system [17]; RCC
histological subtypes were assessed according to the consensus classification of renal cell neoplasia [18,19]. Two specimens of non-neoplastic renal tissue were analysed for comparison.

Routine follow-up procedures consisted of chest X-ray and abdominal ultrasonography annually for pT1/2 cancers and twice a year for pT3/4 or high-grade cancers, respectively. Bone scans and CT were not used routinely. Follow-up data were available for 172 of the 180 patients (96%) with primary RCCs, with a mean (median) follow-up of 26 (24) months, and all with TCC, with a follow-up of 36 (27) months. The survival data were obtained from the Austrian Cancer Registry, which gives not only the date but also cause of death, and allows a distinction between overall and tumour-specific survival. Disease-free survival was assessed by re-evaluating the records at our outpatient clinic; missing data were completed by a mailed questionnaire and telephone interviews with the patients and their physicians.

IMMUNOHISTOCHEMISTRY

For immunohistochemical analysis a tissue microarray (TMA) technique was used which allows staining of many specimens on one slide. TMAs were prepared using a manual tissue-arraying instrument (Beecher, Silver Spring, MD, USA), the details of the technique having been described previously [20]. Three cylindrical core biopsies, 0.6 mm in diameter, were taken from different sites of each tumour and arrayed in a recipient paraffin TMA block. Sections (4 \mu m) were mounted on Superfrost\textsuperscript{TM} slides for immunohistochemical analysis using an automated immunostainer (Dako Autostainer, Universal Staining System, Dako, Glostrup, Denmark). TMA sections were deparaffinized, rehydrated in graded alcohols and treated for 5 min with 1% H\textsubscript{2}O\textsubscript{2}. Sections were submitted to microwave antigen retrieval (20 min, 750 W in Dako Target Retrieval Solution, Code S1699) and then incubated for 30 min with a polyclonal rabbit antihuman CD117 (c-kit) antibody (1 : 1000, Dako, Code A4502). Binding of the primary antibodies was assessed by the Dako ChemMate\textsuperscript{TM} detection kit.

The conditions for immunostaining were optimized using formalin-fixed and paraffin-embedded specimens of GISTs known to show reliable CD117 immunoreactivity. Distinct membranous and cytoplasmic CD117 immunostaining was evaluated as positive. Staining was assessed independently by two pathologists (C.L. and M.R.) according to the criteria of Smithey et al. [21], on an arbitrary scale based on strength: 0, no staining; 1+, weak staining; 2+, moderate staining; 3+, strong staining. Tissue mast cells, which stain 3+, served as a positive control and were used as an internal scoring guide. The distribution of positive cells (pattern) was also recorded in an effort to assess the diffuse or focal nature of immunoreactivity, such that 10% was deemed focal, 11–50%, moderate; and >50%, diffuse. Negative controls included omitting the primary antibody and incubation with Dako ChemMate Antibody Diluent (Code S2022).

RESULTS

The group of primary RCCs comprised 137 (76%) conventional or clear cell tumours, including nine with small foci of sarcomatoid change and four with predominant sarcomatoid morphology showing only small residual foci of conventional carcinoma, 23 (13%) chromophobe tumours and 20 (11%) papillary tumours, including 12 type 1 and eight type 2 tumours. Among the RCC metastases, 55 (95%) were of conventional, two (3%) of papillary and one (2%) of chromophobe subtype. Details of pT categories and tumour grades of primary RCCs and TCCs are shown in Table 2.

Normal renal parenchyma and pelvic transitional epithelium constantly lacked CD117 immunoreactivity, whereas strong

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**TABLE 1** Clinicopathological data of the patients with primary and metastatic RCCs and upper urinary tract TCCs

<table>
<thead>
<tr>
<th>Variable</th>
<th>Primary RCC</th>
<th>Metastatic RCC</th>
<th>TCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>180</td>
<td>58</td>
<td>53</td>
</tr>
<tr>
<td>Sex (male : female)</td>
<td>1.5 : 1</td>
<td>1.4 : 1</td>
<td>1.5 : 1</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean</td>
<td>62.3</td>
<td>63.6</td>
<td>69.5</td>
</tr>
<tr>
<td>median</td>
<td>62.9</td>
<td>65.0</td>
<td>70.3</td>
</tr>
<tr>
<td>range</td>
<td>28–85</td>
<td>39–82</td>
<td>40–88</td>
</tr>
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</table>

**TABLE 2** RCC specimens related to pT categories, tumour grades and histological subtypes

<table>
<thead>
<tr>
<th>pT category and grade, n (%)</th>
<th>RCC</th>
<th>Chromophobe</th>
<th>Papillary</th>
</tr>
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<tbody>
<tr>
<td>Total</td>
<td>137</td>
<td>23</td>
<td>20</td>
</tr>
<tr>
<td>pT1a</td>
<td>50</td>
<td>6 (26)</td>
<td>7 (35)</td>
</tr>
<tr>
<td>pT1b</td>
<td>21</td>
<td>3 (13)</td>
<td>4 (20)</td>
</tr>
<tr>
<td>pT2</td>
<td>5</td>
<td>3 (13)</td>
<td>3 (15)</td>
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<tr>
<td>pT3a</td>
<td>27</td>
<td>6 (26)</td>
<td>4 (20)</td>
</tr>
<tr>
<td>pT3b</td>
<td>34</td>
<td>5 (22)</td>
<td>2 (10)</td>
</tr>
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<td>G1</td>
<td>18</td>
<td>0</td>
<td>1 (5)</td>
</tr>
<tr>
<td>G2</td>
<td>71</td>
<td>14 (61)</td>
<td>13 (65)</td>
</tr>
<tr>
<td>G3</td>
<td>44</td>
<td>9 (39)</td>
<td>6 (30)</td>
</tr>
<tr>
<td>G4</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**TABLE 3** Upper urinary tract transitional cell carcinoma (TCC) specimens related to pT categories and tumour grades

<table>
<thead>
<tr>
<th>pT category and grade, n (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pT1</td>
<td>22 (42)</td>
</tr>
<tr>
<td>pT2</td>
<td>9 (17)</td>
</tr>
<tr>
<td>pT3</td>
<td>22 (42)</td>
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<tr>
<td>G1</td>
<td>0</td>
</tr>
<tr>
<td>G2</td>
<td>28 (53)</td>
</tr>
<tr>
<td>G3</td>
<td>25 (47)</td>
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</table>
cytoplasmic staining of stromal mast cells was detected in all cases (Fig. 1A). For RCCs, immunoreactivity for CD117 was detected in two of 23 (9%) chromophobe tumours, with both a moderate strength and pattern of immunostaining (Fig. 1B). Tumour stage (and size) of these two cases were pT1 G2N0M0 (1.3 cm) and pT1 G3N0M0 (1.8 cm), and both patients were free of disease after 27 and 19 months of follow-up, respectively.

DISCUSSION

The recent development of small molecules, e.g. imatinib mesylate, designed to target specific receptors or pathways for controlling cell growth has resulted in the additional use of immunohistochemistry beyond assisting in histopathological diagnosis. Thus, the immunohistochemical evaluation of Kit expression currently serves as the standard for identifying patients who might benefit from imatinib mesylate treatment [22].

For RCCs, Yamazaki et al. [14] recently investigated 10 conventional, three chromophobe and two papillary carcinomas, reporting Kit immunoreactivity and c-kit up-regulation by gene-expression profiling specifically in the chromophobe tumours. Based on these few cases, the authors concluded that Kit could be both a useful marker and a possible therapeutic target in chromophobe RCCs. The present study confirmed the lack of Kit expression in conventional and papillary carcinomas. However, from the present data, Kit immunoreactivity is only infrequent in chromophobe RCCs. Moreover, as this rare subtype is associated with a more favourable prognosis [23], metastatic cases will only exceptionally be encountered. Finally, the overall rare expression of Kit in TCCs, which to the best of our knowledge is shown in the present study for the first time, shows that routine screening of tumour tissues for Kit by immunohistochemistry may be cost-ineffective.

It is possible that the rare immunoreactivity in our series is related to the staining protocol. However, Kit immunostaining is an optimized and routine staining procedure in our laboratory, and the constant, strong immunoreactivity of stromal mast cells, which served as internal controls, confirmed its diagnostic value. The polyclonal anti-Kit (CD117) antibody used is widely applied to assess Kit expression in formalin-fixed paraffin-embedded GIST specimens in clinical imatinib mesylate trials, and is the most reliable of the anti-Kit antibodies commercially available for immunohistochemistry [24]. Finally, we decided not to use RT-PCR for c-kit mRNA to substantiate our results, as contaminating stromal mast cells would cause false-positive results [14].

In summary, the lack of substantial Kit (CD117) immunoreactivity in both RCC and upper urinary tract TCC does not provide a rationale to investigate imatinib mesylate therapy in clinical trials including patients with advanced disease.

ACKNOWLEDGEMENTS

The authors are grateful to Mrs Gogg-Kamerer, Ms. M. Lindbauer, Ms. A. Sommersacher, Mr M. Al-Effah and Mr R. Christoph for excellent technical assistance.

CONFLICT OF INTEREST

None declared.

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Abbreviations: TMA, tissue microarray; SCF, stem cell factor; GIST, gastrointestinal stromal tumour; PDGFR, platelet-derived growth factor.
Surgery for localized prostate cancer after renal transplantation

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OBJECTIVE

To investigate the feasibility of perineal radical prostatectomy (RP) in renal transplant recipients with localized prostate cancer.

RESULTS

All seven patients successfully tolerated RP with no major complications. The mean (so, range) age at surgery was 62.3 (2.5, 55–74) years and the mean interval from renal transplant to RP 86.5 (25.25, 24–192) months. There was no evidence of increased blood loss, operative duration, transfusion requirement, hospital stay or deterioration of graft function. The presence of an allograft did not alter the surgical approach or management of the patients after RP. The mean follow-up was 22 (2–130) months and all seven patients were followed. One patient had evidence of biochemical recurrence with no radiographic evidence of metastatic disease. Serum prostate-specific antigen was undetectable in the remaining patients.

CONCLUSION

A perineal RP in renal transplant recipients for treating localized prostate cancer offers many advantages over other treatments.

KEYWORDS

prostate cancer, renal transplant, surgery

INTRODUCTION

The successes in renal transplantation have led to liberal criteria for transplant recipients, in that almost 10% of all transplant recipients in the USA are >50 years old [1]. The calculated half-life for grafts from living donors between 1988 and 1996 was 21.6 years [2]. Advances in immunosuppressive therapy in the last two decades have led to a substantial improvement in graft and patient survival after renal transplantation. As more older men are being considered for renal transplantation, and men are living longer with functional allografts, it is inevitable that urologists will encounter more renal transplant recipients with prostate cancer.

The incidence of prostate cancer in the renal transplant population is difficult to interpret because most transplant registry data were obtained before the existence of systematic screening. In the last update of the Cincinnati Transplant Tumor Registry and the Australian and New Zealand Transplant Registry there was a lower incidence of prostate cancer than in the general population [3,4]. However, in the European Nordic countries the frequency of prostate cancer was much higher [5]. It is impossible to draw significant conclusions from these registries because most patients were not screened before or after their renal transplant. However, when patients were routinely screened with PSA testing and/or a DRE the incidence of prostate cancer appeared to be higher than in the general population [6]. In another series, Malavaud et al. [7] reported on 120 consecutive men receiving a renal transplant, who were >50 years old and who were routinely screened with PSA. The incidence of prostate cancer in this selected group was 5.8%. Kinahan et al. [8] reported the incidence of prostatic carcinoma in 390 men on immunosuppression undergoing TURP to be 30%; this is three times higher than the commonly reported rate for patients undergoing TURP. Excluding the data from the transplant registries, when patients are systematically screened it appears that long-term immunosuppression may affect the incidence of prostate cancer.

Immunosuppression, the presence of a pelvic renal graft and the potential for future transplants in the event of graft failure are all factors that must be considered when managing prostate cancer after renal transplantation. In the largest reported series of patients with prostate cancer after organ transplantation, more were found to have localized disease at the time of diagnosis than in the general population, and aggressive interventions were recommended [9]. We present our experience of renal transplant recipients with localized prostate cancer, and the advantages of radical prostatectomy (RP), specifically perineal.

PATIENTS AND METHODS

The study included seven consecutive renal transplant recipients who had a perineal RP between May 1991 and February 2004. All available clinicopathological data were reviewed; two men presented with an abnormal DRE and the rest with elevated serum PSA levels (Tandem R, Hybritech, San Diego, CA). The diagnosis was confirmed on TRUS-guided prostate biopsy. Clinical and pathological staging was assigned using the 2002 TNM guidelines. Radionuclide bone scintigraphy and cross-sectional imaging was reserved only for patients with a PSA level of >20 ng/mL, suspicion of locally advanced disease or the presence of poorly differentiated cancer on needle biopsy (Gleason score >8). None of the patients in this series received preoperative hormone or radiation therapy.
Patients underwent a standard perineal RP by one surgeon (A.M.) using the Belt approach, as previously described [10,11]. Pelvic lymph node dissection was reserved for patients only if the risk of lymph node positivity was >3%, using available prediction models [12,13]. After RP the patients received standard routine care, including immediate return to diet (as tolerated), ambulation and the on the evening after surgery, immediate resumption of their immunosuppressive regimen. The Penrose drain was removed 1 or 2 days after RP, depending on the volume of drainage, and the patients discharged home with the Foley catheter in place, usually 2 days after RP; the Foley was removed 9 days after RP.

The follow-up consisted of a physical examination, including a DRE and serial serum PSA measurements every 3 months. ‘PSA failures’ were defined as men with a PSA of >0.4 ng/mL and increasing after three consecutive measurements. A follow-up was obtained in all seven patients.

RESULTS

The mean (SD, range) age of the men at surgery was 62.3 (2.5, 55–74) years, and the mean interval from renal transplant to RP 86.5 (25.25, 24–192) months. Six patients had a cadaveric transplant and one a living related transplant before RP; the preoperative characteristics are listed in Table 1.

All seven patients successfully tolerated RP with no pelvic lymph node dissection and no major complications. There was one minor complication in one patient, with prolonged gross haematuria requiring a transfusion of red blood cells and periodic gentle bladder irrigation. The mean estimated blood loss was 492.9 (176.8, 100–1500) mL, the total mean operative duration 92.7 (4.1, 83–115) min and the hospital stay 2.6 (0.0.4, 2–5) days. Using serum creatinine as a measure of graft function, none of the men had worsening graft function; all were discharged with unchanged creatinine levels.

The pathological characteristics of the tumours are also shown in Table 1. Currently, one patient has evidence of biochemical recurrence with no radiographic evidence of metastatic disease. This patient’s PSA nadir was 0.4 ng/mL and has subsequently increased to 0.9 ng/mL, 9 months after RP. Serum PSA was undetectable in the remaining patients; the mean follow-up was 22 (2–130) month.

DISCUSSION

Surgery in the present patients was the preferred method of treatment, specifically using the perineal approach. Bladder descent was not impaired by the allograft or by the ureteric reimplantation and a tension-free vesico-urethral anastomosis was easily achieved. There was no increased blood loss, operating time, transfusion requirement or hospital stay in the present series, compared with other contemporary series of patients undergoing RP with no previous transplant [14,15]. All the present patients returned to their baseline creatinine before discharge, and only one required a blood transfusion. There were no major complications and only one minor complication, persistent gross haematuria that resolved with conservative management.

In this series two patients had positive surgical margins; both were focal and located at the apex of the prostate. Large contemporary series comparing perineal and retropubic RP have reported no significant differences in margin positivity rates [14,16]. Even though there were few patients in the present series, the margin positivity rate (two of seven) is comparable with large RP series in untransplanted patients [17].

A retropubic RP is also safe in patients after transplantation [8,18,19]; in the various case reports surgeons were able to perform retropubic RP by modifying the placement of the retractors away from the renal graft, limiting mobilization of the peritoneum ipsilateral to the allograft and with the need to catheterize the ureter to identify the ureteroneocystostomy However, we feel this approach subjects the transplant ureter and renal allograft to potential risk. Graft failure is a serious complication and associated with a high mortality rate. After graft failure the patient survival at 5 years is 57–64% [20]. The current consensus is that perineal RP offers a similar outcome for potency, continence and cancer control when compared with

<table>
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<tr>
<th>Variable</th>
<th>Patient</th>
<th>1</th>
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<td>74</td>
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<td>57</td>
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<tr>
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<tr>
<td>Tumour volume, %</td>
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<td>10</td>
<td>25</td>
<td>20</td>
<td>10</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

*Evidence of biochemical recurrence; LR, living related; C, cadaveric; Cy, Cyclosporin; Tac, tacrolimus; P, prednisolone; MM, mycophenolate mofetil; S, sirolimus.

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retropubic RP [14,15,17]. With this in mind, the perineal approach is more feasible because it avoids any manipulation of the renal graft or transplant ureter, thereby reducing the chances of harm.

Another important issue to consider when treating renal transplant patients is the risk of future graft failure. The lifetime risk of graft failure and need for subsequent repeat transplantation is up to 33% [2]. Thus, a significant proportion of transplant patients will have a repeat transplant; in the USA in 2001, 13% of all transplants were repeats [1]. The retropubic approach facilitates the site of future transplants, typically the contralateral iliac fossa, thereby potentially increasing the complication rates of future transplants. You et al. [21] described a patient who successfully had a cadaveric renal transplant after a perineal RP 3 years earlier, with no complications. However, there are no studies that have reviewed the risks of renal transplant after a retropubic RP. We think that a previous retropubic RP with or without pelvic lymph node dissection could complicate placing a renal graft, and thus we favour the perineal approach, because it preserves the bladder and contralateral iliac fossa for future transplants.

Aggressive therapeutic interventions in the appropriate clinical setting should not be withheld in renal transplant patients with prostate cancer. Age, general state of health, clinical stage, serum PSA and Gleason sum remain critically important in determining the proper treatment for localized prostate cancer. Advances in renal transplantation have improved patient survival considerably, in that untreated prostate cancer could contribute to patient morbidity and possibly mortality. Male transplant recipients in the USA aged 50–54 years have a remaining life-expectancy of 14–19 years [1]; the better life-expectancy seen with current renal transplant patients favours the treatment of localized prostate cancer. Although patients can be monitored closely with interval serum PSA assays, as the accuracy of serum PSA does not appear to be affected by end-stage renal disease or immunosuppression, expectant management was not recommended in the present patients [22]. The natural history of prostate cancer in the immunosuppressed patient is unknown but there is mounting evidence to indicate that immunosuppression may enhance malignant cell growth; it increases the risk of neoplasia by three to five times that in age-matched controls in the general population [23]. In a retrospective review of 1297 renal transplant patients with pre-existing tumours, most recurrences were within 2 years, correlating with the initiation of immunosuppression [24]. Furthermore, 52% of the patients treated >5 years before transplantation died from metastatic disease within 2 years of the transplant, raising the possibility that immunosuppression may have stimulated the growth of dormant metastases. There are no comprehensive studies that have addressed the effect of long-term immunosuppression on prostate cancer; although in the largest series (18 patients) those presenting with advanced or metastatic disease progressed more rapidly than the general population, and the therapy tended to fail earlier than in patients not immunosuppressed [9]. Expectant management with a patient on immunosuppressive therapy has the potential for a poor outcome and was not recommended to any of the present patients. Until there is definite evidence that immunosuppression has no adverse effects on prostate cancer, we consider that watchful waiting should be reserved for highly selected patients.

Radiation therapy via external beam or brachytherapy is another option available for treating prostate cancer after a renal transplant, but currently there are no studies on this subject. Radiation therapy was not recommended in the present series because of the potential risk of radiation nephritis to the allograft, as it is close to the targeted site and risks radiation injury to the bladder, particularly at the site of ureteric reimplantation [25]. Primary androgen ablation is another option but there are no long-term studies available and it was not recommended to any of the present patients. A laparoscopic retropubic RP also was not considered because it was the felt that the presence of the allograft in the iliac fossa would alter the placement of trocars, significantly complicating the surgical technique.

Hormone ablation, surgery, watchful waiting or radiation therapy are all used for managing prostate cancer; the decision for each treatment is based on each patient’s clinical situation. Even though a retropubic RP can be safe in a patient after a renal transplant, we feel that the perineal RP offers specific advantages in this unique clinical situation.

CONFLICT OF INTEREST

None declared.

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Abbreviations: RP, radical prostatectomy.
Neither α-blocker therapy nor cystography is required before early catheter removal after radical prostatectomy

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Accepted for publication 1 October 2004

OBJECTIVE
To evaluate the success of early catheter removal from men after radical retropubic prostatectomy (RRP) without using either cystography or giving an α-blocker.

PATIENTS AND METHODS
We retrospectively analysed 156 consecutive patients who had RRP between June 2003 and May 2004 to determine the incidence of urinary retention after early catheter removal, with no cystogram or using an α-blocker.

RESULTS
The mean age of the men was 60 years and 99% were clinical stage T1 or T2; 74% had their catheters removed 8 days after RRP. The incidence of urinary retention was 1.3%, and of haematuria requiring catheter replacement 2.6%. Two patients (1.3%) developed a bladder neck contracture.

CONCLUSIONS
In the present study removing an indwelling catheter 1 week after RRP was safe, with a minimal risk of urinary retention or bladder neck contracture. The addition of an α-blocker is unlikely to reduce the already low incidence of urinary retention.

KEYWORDS
prostate cancer, radical prostatectomy, catheter removal

INTRODUCTION
After radical retropubic prostatectomy (RRP) an indwelling catheter is required to allow the vesico-urethral anastomosis to heal, and typically this catheter has been left in situ for 3 weeks. Many surgeons have shown the safety of shorter periods of catheter drainage. Some take a cystogram before catheter removal to ensure no extravasation at the vesico-urethral anastomosis [1–5]. Patel et al. [6] proposed adding short-term α-blocker therapy before and after catheter removal to decrease the incidence of urinary retention.

We have made some modifications to the classic RRP, as described by Walsh [7]. We use a Pfannenstiel incision, long-acting spinal anaesthesia, spare the bladder neck when possible, and do not routinely place a pelvic drain. We have shown the safety and feasibility of a bladder neck-sparing RRP [8–11]. In the present study we analysed 156 consecutive RRRPs to determine the incidence of urinary retention after catheter removal 1 week after RRP, without taking a cystogram or using an α-blocker.

PATIENTS AND METHODS
Between June 2003 and June 2004, 156 consecutive men underwent RRP by one surgeon (M.S.S.) at the authors’ institution, and the Institutional Review Board approved a retrospective chart review and analysis. The RRP was as originally described by Walsh [7], with some modifications; we use a bladder neck-sparing RRP whenever possible [11]. Briefly, after the seminal vesicles and vasa have been isolated and mobilized, and the superior prostatic pedicles divided, we circumferentially dissect the prostate from the circular bladder neck fibres. We attempt to maintain the integrity of the bladder neck. On completing the dissection, the bladder neck is usually patent enough to easily accept a 20 F Foley catheter for postoperative drainage. We make the anastomosis with seven 2/0 poliglecaprone sutures. The mucosa is not everted. We do not routinely place a pelvic drain after RRP [12]; it is placed only if there is extravasation at the vesico-urethral anastomosis while filling the bladder with sterile saline after the anastomotic sutures are tied.

All patients returned to the office 1 week after surgery for catheter removal. We did not take a cystogram, or provide patients with an α-blocker before catheter removal. All patients were instructed to attend for a follow-up at 6 weeks and then every 3 months. All perioperative complications were recorded in a database maintained by a statistician (S.S.K.).

RESULTS
Before 1996 we typically removed catheters 14 days after RRP and between 1996 and June 2003 we removed catheters 10 days after RRP. Since then we have attempted to remove all catheters 1 week after RRP and limited the analysis to these patients since June 2003; Table 1 describes the characteristics of these patients. The mean age of the patients was 60 years and 99% were clinical stage T1 or T2. The mean (SD) follow-up was 3.9 (3.4) months.

If there was a large median lobe or the patient had a previous TURP then some reconstruction at the bladder neck was necessary; this was the case in 13 (8%) of the patients. In these patients the mean PSA concentration was 8.9 ng/mL, the mean Gleason score 6.3 and four men (2.6%) had positive margins at the bladder neck.

The catheters were removed 6–8 days after RRP in 74% of men (9% after 9 days, 8% after 10 days, and 5.1% after 11–14 days). Although we attempted to schedule all catheter removals 1 week after surgery, some patients returned later because of office scheduling and logistics. A few patients returned to their primary urologist for catheter removal, and their catheters were removed at their primary urologist's
discretion. We were unable to establish exactly when the catheter was removed for six patients (3.8%).

The incidence of urinary retention, haematuria/clot retention and bladder neck contracture was low (Table 1); there were no re-admissions. Two patients with an anastomotic stricture had a transurethral incision of the concentric narrowing, and both are currently voiding well and continent.

DISCUSSION

An indwelling catheter is placed after RRP to allow the vesico-urethral anastomosis to heal with no serious urinary extravasation. The duration of catheterization is often a concern to the patients; not only is the catheter a source of anxiety, but it causes substantial discomfort [2], so there is an impetus to reduce the duration of catheterization. In an early study, Dalton et al. [13] evaluated 55 men, using cystography, starting 8 days after RRP, when 22% of the catheters were removed because there was no extravasation at the vesico-urethral anastomosis. Those with extravasation had a repeat cystogram until no extravasation was identified and the catheters could be removed. The incidence of urinary retention was 9%. In a larger study, Lepor et al. [2] reported the safety of catheter removal 7 days after RRP, as long as cystography showed no extravasation; 75% of 184 men had negative cystograms and had early catheter removal, but 15% of these developed urinary retention requiring replacement of a catheter.

Santis et al. [14] reported a retrospective analysis of 118 consecutive patients who had catheters removed 8–9 days after RRP. These authors did not take a cystogram before catheter removal, but based the safe removal of the catheter on there being no persistent urinary leak (drains removed by 5 days after RRP), pelvic haematoma, rectal injury or severe obesity. Catheters were removed 8–9 days after RRP in 100 men (85%); urinary retention occurred in 2%, and 9% had a symptomatic bladder neck contracture requiring either dilatation or endoscopic incision.

Advances in laparoscopic RP have allowed some surgeons to remove the catheter 2–4 days after RRP, provided that a cystogram shows no extravasation [15]. In a series by Nadu et al. [15], 10.4% of patients with negative cystograms who had their catheters removed 2–4 days after RRP developed urinary retention. The authors were able to replace the catheters in all patients without cystoscopy. The authors noted that their success in early catheter removal might be related to a continuous running vesico-urethral anastomosis. A recent study by Patel and Lepor [16] evaluating the efficacy of catheter removal 3–4 days after open RRP, showed what the authors considered an excessive rate of urinary retention and complications. Of 151 men evaluated by a cystogram, 25% were not eligible for catheter removal 3–4 days after RRP because of extravasation, and 19.3% of men whose catheters were removed 3–4 days after RRP required emergency replacement of the catheter for urinary retention. Two patients (9% of those men with urinary retention) required re-exploration for complications related to difficulty in placing the catheter. Anastomotic stricture was reported in 12% of men who had early catheter removal; those whose catheters were not removed until 14 days after RRP had a 23% incidence of anastomotic stricture. The authors concluded that cystography and catheter removal should be delayed until at least 7 days after RRP to decrease the risk of urinary retention. Conversely, Little et al. [1] reported a small, prospective pilot study evaluating early catheter removal after RRP. Cystograms were taken in 31 patients 3–4 days after RRP; 87% of those men showed no or minimal extravasation and had their catheters removed within 24 h (mean 4.2 days after RRP). Two (7%) patients developed either gross haematuria or clot retention, and none developed urinary retention. Similarly, Koch et al. [5] reported on the safety of early catheter removal in a series of 365 men. All patients had cystoscopy 3–4 days after RRP; of 72% of men eligible for early removal, urinary retention, clot retention and bladder neck contracture developed in 3.6%, 1.9% and 1.7%, respectively.

In an updated series, Patel et al. [6] evaluated the efficacy of tamsulosin in reducing the incidence of urinary retention after early catheter removal. Tamsulosin 0.4 mg was administered daily to patients from 3 days before until 4 days after catheter removal. There was a significant difference in the incidence of urinary retention between these patients (2.6%) and an earlier cohort who did not receive tamsulosin (10%). The authors concluded that tamsulosin should be administered to all patients when removing the catheter within 8 days after RRP. However, this was an unrandomized study comparing two sequential groups of patients, so the results might have been influenced by changes in surgical technique.

In the present study, we attempted to remove all catheters 1 week after RRP without taking a cystogram. The incidence of urinary retention, clot retention and bladder neck contracture was 1–2% (Table 1). We consider that men who have RRP with bladder neck-sparing are not at high risk of vesico-urethral anastomotic leakage and urinary retention. The few men who developed retention were easily catheterized with no need for cystoscopy.

The main limitation of the present study is that it was not randomized. However, based on other authors’ work on the safety of early catheter removal and our initial impressions, we felt that it was safe to initiate catheter removal 7 days after RRP in these patients. We do not think that an a-blocker is required to decrease the risk of urinary retention. We think that bladder neck-sparing aids in allowing for early catheter removal. Although the present follow-up is short, we do not consider that more anastomotic strictures will

### TABLE 1 Characteristics of the study patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%) or mean (SD)</th>
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<tr>
<td><strong>N patients</strong></td>
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<td><strong>Clinical stage, n (%)</strong></td>
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EARLY CATHETER REMOVAL AFTER RADICAL PROSTATECTOMY

Develop in the future, as this complication usually occurs within 3 months.

Removing the indwelling catheter 1 week after RRP is safe, with a minimal risk of urinary retention or bladder neck contracture. Our technique of bladder neck-sparing reduces the need for cystography to exclude extravasation before catheter removal. Adding an α-blocker is unlikely to reduce the already low incidence of urinary retention.

CONFLICT OF INTEREST

None declared.

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Abbreviations: RRP, radical retropubic prostatectomy.
Lower Urinary Tract

The first paper in this section is a review by several highly respected authors of diagnostic criteria for evaluating patients with symptomatic stress urinary incontinence, and is followed by a review of the role of urgency and its measurement in the overactive bladder symptom syndrome, with emphasis on current concepts and future prospects. These are two important papers, which point the reader in the direction of a greater understanding of these conditions.

The concept of α-blockade before a trial without catheter after acute urinary retention is revisited by authors from the UK, who used tamsulosin in a randomized controlled trial. They found that it is appropriate to recommend tamsulosin for such use in this condition.

A critical review of diagnostic criteria for evaluating patients with symptomatic stress urinary incontinence

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INTRODUCTION

The minimum evaluation criteria necessary to diagnose stress urinary incontinence (SUI) have recently been the subject of debate, especially for the use of urodynamics and the type of treatment contemplated (e.g. conservative or surgical management). The concept of minimum evaluation is important, given that some tests are expensive, unavailable in certain countries, inconvenient for the patient and possibly of doubtful usefulness in indicating therapeutic strategy.

Currently, there is no adequate consensus on how to diagnose SUI or categorize the disorder in terms of the two principal postulated pathophysiological mechanisms; intrinsic sphincter deficiency (ISD) and urethral hypermobility. These represent extremes of a spectrum, and coexist in the vast majority of patients. An inherent problem in current practice is the poor understanding of the pathophysiological basis for female continence.

In August 2003, an international panel met to discuss the different diagnostic tests for SUI and to reach a consensus on (i) the individual diagnostic tests, evaluating their use in clinical practice vs clinical trials or research, and (ii) the minimum diagnostic assessment needed before initiating conservative, noninvasive therapy (behavioural therapy, pharmacotherapy, pelvic floor training, vaginal devices and injectable agents). Injectable agents may not be deemed by some to be noninvasive, instead being described as minimally invasive, but they clearly do not alter further treatment, or unless significant complications arise, produce new problems. A further aim was to discuss the classification of SUI. The outcome of this meeting is presented in this review.

DATA SELECTION

Experts reviewed the published reports on diagnostic methods for SUI and presented
their findings for discussion. Data were obtained from various sources including the ICS [1], the 2nd International Consultation on Incontinence (ICI) [2], and by searches of Medline for articles published between 1966 and 2003. The main Medline search used the term ‘stress urinary incontinence’ and the following: ‘diagnosis’, ‘urodynamic’, ‘urodynamics’, ‘history’, ‘urethral pressure’, ‘leak-point pressure’, ‘Q-tip’, ‘pad’, ‘residual’, ‘cystometry’, ‘cystography’, ‘cystourethrography’, ‘video’, ‘ultrasound’ and ‘sonography’, ‘frequency volume chart’ or ‘frequency volume charts’, ‘incontinence’ and ‘test’. The ICS website was searched for abstracts published at the Annual meetings between 1999 and 2002 in the ‘urodynamics’, ‘stress incontinence’ and ‘diagnostic techniques’ categories. In all, 2554 references/abstracts were identified, of which 502 met the search criteria of relevance to diagnostic methods, and form the basis of this review. Supplementary references were identified.

**DIAGNOSTIC TESTS FOR SUI**

**SYMPTOMS, HISTORY AND QUESTIONNAIRES**

Involuntary leakage of urine on effort or exertion, or on sneezing or coughing, is the most commonly used definition in clinical practice on which to select a treatment [3]. Epidemiological studies, most using this definition, show that SUI occurs in a mean (range) of 49 (24–75)% of patients with UI, while mixed incontinence occurs in 29 (11–61)% [4].

SUI is easily recognized by assessing the patient’s history, but there is no practical, validated tool to quantify symptom severity. The Stamey classification [5], used in many publications, is simplistic and of limited use, while alternative symptom/quality-of-life scoring systems (e.g. Bristol Female Urinary Tract Symptom questionnaire [6], Continifem™ scale [7], King’s Health Questionnaire [8]), all good research tools, are perceived by many to be too complicated for clinical practice.

Although a careful review of the patient’s history is essential, it may underestimate the true prevalence of SUI, as shown in the study by Sandvik et al. [9], in which patient history was validated using a urodynamic evaluation. The validation altered the apparent prevalence of SUI from 51% to 77%, mainly attributable to fewer patients with mixed incontinence. Conversely, a classification based on urodynamics rather than symptoms may not accurately reflect what bothers the patient. Clearly, a combination of these approaches may provide optimum accuracy.

The relationship between SUI and the overactive bladder (OAB) syndrome is important. It is artificial to differentiate between the urethra and bladder, with experimental evidence suggesting a link between the structures (e.g. urethral perfusion of saline provokes bladder contraction in animal models [10,11]). Moreover, clinical evidence suggests some overlap between SUI and OAB, albeit that current definitions would support the possibility that OAB needs to be considered when urinary frequency is a bothersome complaint. Cardozo and Stanton [12] reported that many women with urodynamic SUI also had urgency/frequency symptoms (e.g. urge incontinence, 55%). This proposed overlap may mean that certain patients with OAB could benefit from treatments directed at the urethra, and that prevalent SUI associated with OAB is not a contraindication to surgery. Indeed, improvements in OAB have been reported when concurrent SUI is treated, i.e. those cases in which detrusor overactivity is precipitated by acutely increased intra-abdominal pressure (e.g. Valsalva manoeuvre) [13].

**CLINICAL EXAMINATION**

This is the most commonly used method for diagnosing SUI. A general physical examination comprises an assessment of patient cognition, dexterity and ambulation (especially in the elderly), and a targeted neuro-urological examination to detect systemic neurological disease and local neuro-urological problems. The utility of neuro-urological examination has never been formally investigated in ambulatory women with pure/predominant SUI, but common sense supports its routine use.

A directed pelvic examination is of critical importance. Gluteo-sacral region abnormalities and discrete fascial defects can be detected, while examination with a speculum can identify abnormalities such as cancer and urethral diverticula; a bimanual examination can identify pelvic masses. Pelvic muscle strength and integrity can be assessed, with the Brinks scale being commonly used [14]. However, there is scant published evidence validating the use of muscle-strength scores. Pelvic support assessment is another option, with recognized scales being used; Baden-Walker [15]; and pelvic organ prolapse-quantified (POP-Q), in which the stages have been arbitrarily designated [16]. The Baden-Walker system is generally easier to use, although there are concerns over its utility in assessing anterior and posterior wall support, while the reproducibility of the POP-Q system has been more extensively validated. The Q-tip test, which has not been validated, aims to evaluate urethrovescical junction (bladder neck) mobility [17], although it is widely considered to be too inaccurate to be clinically useful.

Provocative measures to produce SUI during examination are essential, with cough-stress tests to produce meatal-based urinary leakage, including several variants [18–21]. In general, this test has a high sensitivity for the diagnosis of SUI, but variable specificity.

Clearly, a clinical examination is a vital component of SUI diagnosis, although it is often not feasible to replicate the position and circumstances in which the patient actually leaks. The utility of specific aspects is generally not well studied, especially in patients with POP.

**OBJECTIVE LEAKAGE MEASURES**

Frequency/Volume charts, or voiding/bladder diaries, are used to record voided volumes, urgency, incontinence episodes, pad usage and fluid intake where appropriate. The Larsson nomogram was proposed as an aid when using chart information to distinguish between SUI and detrusor overactivity [22], but its specificity and sensitivity appear to be too low for this purpose [23]. For differentiating between urge incontinence and SUI, the frequency of night-time micturition has been shown to be the most discriminating chart variable [24].

Pad tests are another diagnostic measure, with many variations in use. The resulting lack of standardization is a major disadvantage, and makes reports using the pad test difficult to interpret [25]. Abnormal results have been interpreted as a leakage of >1.4 g/h [analysis of 90 ‘normal’ women [26]] and 8 g/24 h [analysis of 23 asymptomatic women [27]].
Pad tests cannot distinguish between the type or pathophysiology of incontinence, although leakage may be greater with detrusor overactivity than SUI [28]. It has been proposed that short-term tests (1–2 h) are a measure of function, whereas long-term tests (12–48 h) assess symptoms [29]. Although short-term pad tests have lower reproducibility and sensitivity [29], they are easier to perform and the ICS have defined suggested criteria for a 1-h assessment [30]. Pad tests have not been validated in women with POP.

**UROFLOWMETRY, RESIDUAL URINE AND PRESSURE–FLOW STUDIES**

Peak flow rate has been investigated as a screening tool, while residual urine is important in excluding incomplete voiding and overflow incontinence (i.e. leakage of urine at a greater than normal bladder capacity because of detrusor underactivity). These are rare conditions in women without POP or previous incontinence procedures. However, the results of a ‘minimal’ care programme community study suggest that urinary flow rate and residual urine cannot be justified as routine measurements [31].

Pressure-flow studies involve the simultaneous recording of bladder pressure and urinary flow rate, and can, by showing detrusor dysfunction, help to unmask or delineate possible neurogenic dysfunction [32]. It must be recognized that detrusor overactivity may not be evident in symptomatic patients with urge incontinence, and conversely may be seen in asymptomatic individuals. Although there is evidently a good correlation between urodynamical findings during the filling phase and symptoms, it is not absolute.

**IMAGING METHODS**

Cysto-urethrography, pelvic floor ultrasonography and MRI for urinary incontinence were recently reviewed during the 2nd ICI [33].

Cysto-urethrography is the most extensively studied imaging method; it can be used to evaluate both qualitative (e.g. funnelling of the proximal urethra) and quantitative variables (e.g. posterior urethrovesical angle). The degree of change of posterior urethrovesical angle forms the basis of a urethral hypermobility classification system proposed by Green in 1962 [34].

The role of cysto-urethrography alone in female urinary incontinence is yet to be established, and it cannot be recommended for the diagnosis or classification of this condition. Nevertheless, it may be a reasonable option in the preoperative evaluation of complicated/recurrent female UI.

Pelvic floor ultrasonography allows a morphological and functional evaluation of urinary incontinence, although the technique needs to be standardized [33]. Qualitatively, ultrasonography can measure variables such as bladder neck funnelling and position; quantitative variables measured are the retroversical angle β and internal urethral orifice position. This technique is developing rapidly and, theoretically, allows dynamic visualization of urethral and bladder behaviour, and imaging of pelvic floor muscle contraction. It cannot provide a diagnosis of SUI or urge incontinence, and should be considered as investigational [33], although it may assist in diagnosing urethral hypermobility.

Several MRI variations are available to investigate urinary incontinence [33,35], including endovaginal and dynamic techniques. Advantages of MRI include lack of irradiation, speed and the ability to manipulate images after testing, with the major disadvantages being the high cost and lack of universal facilities. To be of maximum value, MRI should be used in the position of leakage. MRI is indicated in assessing female UI and pelvic floor disorders only in very selected cases, and should be considered an investigational technique [33].

Videocystometry/video-urodynamics: cystometry evaluates the pressure-volume relationship of the bladder, with subtracted cystometry used to measure ‘true’ bladder pressure. Videocystometry, first described in the late 1960s [36], involves fluoroscopic visualization of the bladder and urethra in conjunction with simultaneous measurement of vesical and urethral pressures and contrast imaging. It allows visualization of the moment of leakage during cough and straining tests, as well as providing information on variables such as urethral hypermobility and bladder base descent. Video-urodynamics has been considered the reference standard diagnostic technique for UI, but few studies have investigated its use in comparison and correlation with ‘simple’ urodynamics, or with symptoms of lower urinary tract dysfunction. This technique exposes the patient to radiation and is expensive, but is widely accepted to be effective, and provides comprehensive functional and anatomical information.

Current opinion supports the use of video-urodynamics for patients with complex pathology, when the diagnosis is unclear or when previous treatment has failed. It can also help to ensure the correct positioning of pessaries during preoperative screening of certain patients with POP for ‘occult’ SUI [37].

Abdominal leak point pressure (ALPP) is the vesical pressure at leakage during abdominal stress in the absence of detrusor contraction. Abdominal stress may be induced by a cough (CLPP) or a Valsalva manoeuvre (VLPP), with the two stressors differing physiologically, particularly in the rate and nature of the observed pressure rise. Whilst higher abdominal pressures can be achieved with CLPP, the VLPP is better controlled and less variable [32]. Generally, CLPP is used for patients with SUI who do not leak during a VLPP measurement.

For an ALPP to be valid, it is assumed that; the transurethral catheter used does not obstruct the urethra or alter coaptation; straining or coughing does not distort the urethra; and no pelvic relaxation or contraction occurs. However, it is difficult to know whether these criteria hold during the test.

Although the concept of ALPP is empirically sound, its value is limited by a lack of standardized methods. Variations occur in the type of catheter, catheter calibre, bladder volume and patient position. The exact baseline used during the test varies among clinicians, which can make a dramatic difference to the derived ALPP value. A large cystocele will make the LPP appear artificially high, and should be reduced and held in place before testing. LPP tests have not been validated in women with POP.

In theory, a successfully treated patient should not have a measurable ALPP, as they do not leak. Few data are available on the actual magnitude of the change in ALPP after treatment for SUI, and how this correlates with treatment outcome. One general finding is that VLPP does not change significantly if the treatment fails. For example, after a
suburethral sling operation in 30 women, the VLPP increased significantly after a successful operation (mean change 61.1 cmH₂O; P < 0.001) but not after failure (mean change 9.7 cmH₂O, P = 0.226) [38]. Moreover, it is not possible to assign a numerical LPP value that will equate to the cure of patients.

Urethral pressure can be measured either using a catheter-mounted transducer or a fluid-fill system where urethral pressure is equated to the fluid pressure needed to just open a closed (collapsed) urethra [39]. Urethral pressure profilometry (UPP) can be used to measure the maximum urethral pressure, maximum urethral closure pressure, functional urethral length (FUL) and pressure transmission ratio, with urethrocystometry a variant. When reporting UPP data it is important to state the exact method and materials used [40].

Although UPP can potentially be highly informative, it has many problems, the most significant being the large overlap in values between normal and symptomatic patients [41]. UPP does not discriminate SUI from other urinary disorders, or measure severity or return to normal after a successful intervention [42]. Various methods have been developed to improve UPP, including vesico-urethral pressuregrams [43], and cross-sectional area extrapolations [44], but these are research tools unsuitable for clinical practice.

Major factors affecting UPP are the inherently artefactual patient position (not usually upright, the position in which patients normally leak), the transducer position, bladder volume, extent of patient provocation during stress UPP and movement of the transducer during the stress UPP manoeuvre. There are several secondary problems, including the urethral pressure variability during bladder filling and lack of normative values. Lack of reproducibility can also be a problem [45], although not necessarily in specialized and experienced urodynamic laboratories. There is a lack of validation in women with POP.

Other urethral measurements, such as FUL and stress urethral profiles, have been reported to reduce the diagnostic and predictive errors of urethral function, but suffer from similar difficulties; overlap between normal, incontinent and postoperatively continent women, and lack of reproducibility among urodynamic centres.

Overall, UPP is an investigative tool that may provide information about the characteristics of the urethra. The clinical value of UPP, including pressure transmission ratio measurements, is largely unconfirmed, and although prognostic value has been shown in some studies, its actual importance is debatable.

UNDERLINING THE PATHOPHYSIOLOGY IN SUI

Many tests have been used to try and differentiate between urethral hypermobility and ISD. However, such a rigid classification of patients has proven to be controversial, and generated much debate, as it is likely there is a combination of both pathophysiologies in many patients. It was originally proposed that a low ALPP (<60 cmH₂O) or a low MUCP (<20 cmH₂O) is indicative of ISD, but neither of these criteria have a strong evidence base. There is a low concordance between a low ALPP and low MUCP, so the most appropriate method to diagnose ISD is controversial [32]. Attempts have been made to use the supine stress test as a screening tool for ISD [18,20,46], but overall this technique is apparently not sufficiently reliable to be diagnostic in the specific classification of SUI pathophysiology.

The dichotomous classification of SUI into hypermobility and ISD is an oversimplification. In reality, it appears that the two pathophysiologies coexist, as suggested on video-urodynamic studies [47], and form a continuous spectrum. As combined hypermobility and ISD occurs in the vast majority of patients, the challenge is to determine the position of a given patient within the spectrum. The uncertainty over this categorization is recognized by the ICS, which has called for further research in this area [3].

The separation of hypermobility and ISD is important where it may influence treatment outcome. Several studies suggest that a low MUCP or ALPP, indicative of ISD, is predictive of a poorer surgical outcome with a suspension procedure, but overall the data are contradictory, and need clarification [32]. For studies investigating injectable agents, the US Food and Drug Administration (FDA) states that females must have an ALPP of <50–60 cmH₂O [48] (i.e. what the FDA considers indicative of ISD), although a recent registration trial used a value of <50 cmH₂O [49]. However, data show that injectable agents produce similar success rates in patients with ISD or hypermobile SUI [50]. Indeed, in the study by Herschorn and Radomski [51], there was no significant difference in outcome between patients with or without hypermobility.

SUI DIAGNOSIS – A CONSENSUS

EVALUATION OF DIAGNOSTIC TESTS

This review is the first to examine diagnostic techniques for UI in the context of one condition (i.e. SUI). The different techniques are evaluated in Table 1, where the index patient has pure/predominant uncomplicated SUI, no POP, no previous surgery for SUI, and is ambulatory and cognitively intact.

Symptomatic evaluation is of fundamental importance in diagnosing SUI, with diaries being recommended for use in all patients. Interpreting the information is key to an adequate diagnosis (e.g. frequent voiding at night is generally not common in patients with pure/predominant SUI). Diaries are useful tools for educating patients, and reduce the need for questionnaires. Compliance can be a problem, but recent work suggests that a 3-day diary may be as informative as a longer-term assessment [52]. Moreover, a 4-day chart has been shown to be as reliable as a 7-day chart [53]. A comprehensive physical examination is mandatory to assess POP, and neurological evaluation, the use of a speculum and bimanual examination are recommended.

When using observational stress or cough tests, if a patient does not leak when supine, the test should be repeated with the patient upright. Pelvic floor assessments are recommended for routine, clinical study and research use, although they can only provide reliable qualitative rather than quantitative information.

Some opinion supports the routine use of an estimate of postvoid residual volume to exclude large residual volumes as a potential source of leakage or as a potential risk factor for retention after surgery, but this is not unanimously agreed upon.
Pad tests are considered of little benefit in the routine setting. In clinical studies, the lack of standardization is problematical, but they may be useful if patients with POP are excluded, or as a secondary outcome.

ALPP is not recommended for routine use because there is no standardization; it is of benefit when using clearly defined criteria in the research and clinical study setting, but a clear need exists to standardize this test for the future. UPP is standardized in theory but not in practice, and it was agreed that the use of a microtip or fibre-optic catheter was the preferred method.

MRI can give information about anatomical structure (and function if dynamic scanning is used). It is inappropriate for routine use at present and is recommended only in studies to provide an insight into a particular problem.

Pressure-flow urodynamic studies and videocystometry are only advocated in routine practice where it is appropriate to find the exact pathophysiology, particularly before invasive and potentially irreversible procedures. Medicolegal issues may dictate the routine use of cystometry/videocystometry in certain countries.

Subjective 5-level Likert scales (e.g. rating symptoms as worse, unchanged, small improvement, improved or much improved) are of particular relevance in monitoring the success of interventions.

**CONCLUSIONS**

The Second ICI recommended a flow chart for the initial assessment of UI in women [2]; considering the available evidence as reviewed here, we provide additional guidance by proposing an amended flow chart for managing SUI in the index patient [i.e. uncomplicated SUI; Fig. 1].

A clinical examination and assessment of patient history form the basis of SUI diagnosis, with the use of many urodynamic techniques in clinical practice often limited by lack of standardization, complexity and cost. On the basis of current publications, a simple preoperative evaluation is adequate to allow the initiation of conservative, noninvasive therapy. More extensive analysis [i.e.

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**TABLE 1** The evaluation of the different diagnostic tests for SUI, indicating whether they assess structure or function, or are of use in research (i.e. studies into the pathophysiology of SUI), the routine setting (i.e. before instituting conservative or noninvasive therapy) or clinical studies (specifically with injectable agents). The tests are classified into those that may form part of the simple evaluation adequate to initiate conservative, noninvasive therapy in the index patient, and additional investigations as necessary.

<table>
<thead>
<tr>
<th>Test</th>
<th>Evaluates structure</th>
<th>Evaluates function</th>
<th>Research use†</th>
<th>Routine use</th>
<th>Use in studies of injectable agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple evaluation (for conservative, noninvasive therapy)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
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<td>✓</td>
<td>✓✓</td>
<td>✓</td>
<td>✓✓✓</td>
</tr>
<tr>
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<td>✓</td>
<td>✓✓</td>
<td>✓</td>
<td>✓✓</td>
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<td>Questionnaires</td>
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<td>✓✓</td>
</tr>
<tr>
<td>Diaries</td>
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<td>✓✓</td>
<td>✓</td>
<td>✓✓</td>
</tr>
<tr>
<td>Quality of life/bother</td>
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<td>−</td>
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<td>✓</td>
<td>✓✓</td>
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<tr>
<td>Physical examination</td>
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<td>−</td>
<td>✓✓</td>
<td>✓</td>
<td>✓✓</td>
</tr>
<tr>
<td>(POP), including speculum and bimanual</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Physical examination (neurological)</td>
<td>−</td>
<td>++</td>
<td>✓✓</td>
<td>✓</td>
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</tr>
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<td>Stress or cough test</td>
<td>−</td>
<td>✓</td>
<td>✓✓</td>
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<td>Pelvic floor assessment</td>
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<td>+</td>
<td>✓✓</td>
<td>✓</td>
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</tr>
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<td>Post-void residual volume</td>
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<td>✓</td>
<td>✓✓</td>
<td>✓</td>
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</tr>
<tr>
<td>Additional investigations</td>
<td></td>
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<td></td>
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<tr>
<td>Pad test</td>
<td>−</td>
<td>+</td>
<td>✓✓</td>
<td>–</td>
<td>–</td>
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<tr>
<td>ALPP</td>
<td>−</td>
<td>✓</td>
<td>✓✓</td>
<td>–</td>
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</tr>
<tr>
<td>UPP</td>
<td>−</td>
<td>✓</td>
<td>✓✓</td>
<td>–</td>
<td>✓</td>
</tr>
<tr>
<td>Non-invasive uroflowmetry</td>
<td>−</td>
<td>✓</td>
<td>✓✓</td>
<td>–</td>
<td>✓</td>
</tr>
<tr>
<td>Ultrasonography</td>
<td>✓</td>
<td>–</td>
<td>✓✓</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Cysto-urethrography</td>
<td>+</td>
<td>+</td>
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<tr>
<td>MRI</td>
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<td>✓</td>
<td>✓✓</td>
<td>–</td>
<td>✓</td>
</tr>
<tr>
<td>Pressure-flow urodynamics</td>
<td>−</td>
<td>✓</td>
<td>✓✓</td>
<td>–</td>
<td>✓</td>
</tr>
<tr>
<td>Videocystometry</td>
<td>✓</td>
<td>✓</td>
<td>✓✓</td>
<td>–</td>
<td>✓</td>
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<tr>
<td>Cysto-urethroscopy</td>
<td>+</td>
<td>+</td>
<td>✓✓</td>
<td>–</td>
<td>✓</td>
</tr>
<tr>
<td>Electromyography</td>
<td>−</td>
<td>+</td>
<td>✓✓</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Five-level improvement scale (subjective)</td>
<td>−</td>
<td>+</td>
<td>✓✓</td>
<td>–</td>
<td>✓</td>
</tr>
</tbody>
</table>

*+, Limited information/use; †Not a unanimous recommendation; ‡Only recommended in routine use to answer a specific question; †This assessment represents the views of the authors, as any test should be permitted for research use. Urine analysis and assessment of oestrogen status were not evaluated.
urodynamics) is needed in patients with POP and SUI who require more invasive and complex surgical treatment. Furthermore, some index patients may require surgery, or the clinician may deem it appropriate, particularly after failed surgery, in a complex or a critical situation or where neurological disease is evident.

It is clear from existing reports that the appropriate diagnosis of SUI poses many challenges, both in the need to clarify the role of the relative components of ISD and hypermobility, which appear to exist across a spectrum, and to determine their influence on treatment outcome. The availability of newer dynamic and anatomical investigative techniques, such as functional MRI, is anticipated to facilitate an increased understanding of SUI.

CONFLICT OF INTEREST

None declared.

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FIG. 1. Flow chart for managing SUI in the index patient (i.e. uncomplicated SUI with a clear history of incontinence associated with physical activity). *Not a unanimous recommendation; †not evaluated in this review.
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Abbreviations: SUI, stress urinary incontinence; ISD, intrinsic sphincter deficiency; ICI, International Consultation on Incontinence; OAB, overactive bladder syndrome; POP, pelvic organ prolapse; A(C)(V)LPP, abdominal (cough) (Valsalva) leak-point pressure; UPP, urethral pressure profilometry; FUL, functional urethral length; MUCP, maximum urethral closure pressure; FDA, Food and Drug Administration.
The role of urinary urgency and its measurement in the overactive bladder symptom syndrome: current concepts and future prospects

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OBJECTIVE

To review the concept of urinary urgency and its practical measurement in clinical trials, and advance the hypothesis that while urge is experienced by normal people, urgency is always pathological.

METHODS

According to the International Continence Society (ICS) definition, urgency is the primary symptom of the overactive bladder (OAB) syndrome, but in clinical trials there are inconsistencies in both the definition and assessment of urgency. We searched the PubMed and BIOSIS databases for publications and abstracts related to the clinical assessment of urgency in patients with OAB.

RESULTS

The differentiation of urgency from the normal physiological desire to void is discussed. In clinical studies of OAB, urgency has been measured both qualitatively and quantitatively. Existing qualitative assessment scales for urgency are deficient in accuracy, validation or both, and are largely inconsistent with the currently accepted ICS definition of urgency. The quantitative assessment of urgency by diary entry has been validated and may be the most accurate, reproducible and clinically meaningful method available for measuring this variable.

CONCLUSION

Based on the existing ICS definition of urgency as ‘a compelling desire to pass urine that is difficult to defer’, the concept of qualitative assessment of urgency may be flawed.

KEYWORDS

overactive bladder, urgency, measurement of symptoms, frequency, incontinence

INTRODUCTION

The term overactive bladder (OAB), first used in 1997 [1], has developed to become the OAB syndrome (OABS), a term that encompasses the collection of bladder storage symptoms (urgency, frequency, urge incontinence and nocturia) suggestive of detrusor overactivity. The first definition of OAB held that the symptoms of urgency, frequency, urge incontinence and nocturia could ‘occur singly or in combination’ [2]. While descriptive, this definition was suboptimal, as individuals with a single symptom of urinary frequency could be deemed to have OAB when the underlying cause may not have been bladder-related.

The prevalence of symptoms of OAB has been established in large population-based surveys in the USA [3] and Europe [4]. Data from the NOBLE study [3] indicated that up to 60% of those with OAB did not actually have urge incontinence. From the standpoint of symptom bother, urgency, with or without the presence of urge incontinence, had a more significant impact on patient-reported quality of life (QoL) [3], but frequency alone had no significant effect on QoL until patients had >11 voids/day [5]. It was obvious that the definition of OAB required clarification, and that this clarification needed to be based on the primary, or predominant, symptom of OAB.

In 2002, the Standardization Sub-committee of the ICS took into account the need to incorporate patient-reported symptom bother and QoL impact within the definition of OAB. They defined OABS or urgency/frequency syndrome as ‘urgency with or without incontinence, usually with frequency and nocturia’ in the absence of infection or other obvious pathology [6]. This new symptom-based terminology limited detrusor overactivity to a condition that can only be definitively diagnosed by urodynamics study.

The new definition of OAB identifies urgency as the pivotal symptom that patients must experience to have OAB, except for patients who present with no sensation (e.g. complete spinal cord injury). Indeed, only about a third of individuals with urgency have coexisting urge incontinence, but almost all have coexisting frequency (Fig. 1).

This new ICS definition of OAB provides greater clarity, but making urgency the pivotal symptom of OAB requires that urologists can describe and measure it reliably. Integral to this process is the need to discriminate between urgency episodes, which are pathological, and the normal urge, or desire to void.

UNDERSTANDING ‘URGE’ AND DEFINING URGENCY

Given the central importance of urgency to the definition of OAB, it is imperative that urgency itself be carefully defined. According to the ICS, urgency is ‘the complaint of a sudden compelling desire to pass urine, which is difficult to defer’ [8]. This definition excludes the desire to void to avoid pain or leakage that was included in the earlier definition, but now includes an element of necessity that is not associated with voluntary voiding [2]. It is important to differentiate between ‘urge’, which is a normal physiological sensation, and urgency, which we consider pathological. Central to this distinction is the debate over whether urgency is merely an extreme form of ‘urge’. If this were a continuum, then normal people could experience urgency, but in the model we propose, urgency is always abnormal. However, patients with OAB can have both ‘urge’ and urgency, and not every micturition episode is associated with urgency. The challenge to researchers is to be able to differentiate ‘urge’ from urgency in patients with OAB and to describe urgency to such patients clearly enough for them to record it accurately in diaries.

The definition of urgency has two components: one is quantitative and identifies the episodes of urgency, which can be counted, and the other qualitative, which refers to the patient’s inability to defer voiding once the sensation of urgency is perceived. In other words, urgency demands attention and action. Each element dynamically affects the patient’s perception of treatment of OAB and their willingness to stay on therapy.

Thus, urgency, the sudden and compelling desire (or ‘urge’) to void, is a sensation which by its definition is episodic and maximal. Therefore, it is unnecessary to characterize this portion of the definition with measurements of intensity. The presence of a ‘sudden, compelling desire’ is similar to a light switch; it is either on or off. The need to void that accompanies urgency is quite distinct from the physiological sensation characteristic of bladder filling, which can be tolerated. This physiological sensation is defined as the ‘urge’, or desire to void. The desire to void can vary in intensity, and its measurement is of great interest in assessing symptom severity and the outcome of therapy; however, its clinical utility needs to be evaluated. Because urgency is episodic it can be quantified by counting, as is done for frequency and incontinence episodes using a voiding diary.

Figure 2 shows the schema of how ‘desire to void’ as a symptom of bladder fullness might be considered in relationship to the time of a void and hence the interval between voids. Filling cystometry experiments with normal subjects indicate that as the bladder fills, a reproducible series of sensations or increasing desire to void is experienced [7,8]. Their duration, intensity and frequency will be variable but will increase in relation to increasing bladder volume. Recent work has shown that the intensity of this sensation depends on bladder volume. Oliver et al. [9] allowed patients with OAB to grade ‘urge’ with a five-button keypad during filling and emptying of the bladder. ‘Urge’ scores were defined as (0) none, (1) mild, (2) moderate, (3) strong, and (4) desperate. During a pseudo-random sequence of bladder filling and emptying, urge scores were reproducible and strongly correlated with bladder volume, regardless of the direction of volume change [9]. At some point during bladder filling, based on individual circumstances at that time, a normal, controlled voluntary void will occur. The volume at which this occurs is called the functional bladder capacity. The ‘urge’ sensation is likely to be episodic but can resolve or be suppressed, and then recur before a void takes place. The ability to defer voiding is key to the definition of ‘urge’ and consequently results in a variable interval between voids in normal individuals [10]. For example, with the same individual in the home, the functional bladder capacity might be different than at work, based on the availability of time, bathroom facilities and level of distraction.

Figure 3a shows a schematic of the equivalent situation in a patient with OAB. Such a patient will also experience a desire to void similar to that in normal individuals, but when urgency episodes occur they are different because they persist, albeit episodically, until a void.

![FIG. 1. The relationship between the different symptoms of OABS. While not to scale, the figure indicates the relative magnitude of symptom prevalence and the overlap of OABS symptoms [2].](image1)

![FIG. 2. A schematic of the relationship between bladder volume and desire to void during the normal micturition cycle. During the normal cycle, desire to void (urge) is intermittent and increases with bladder volume. The cycle terminates with a void that may or may not be associated with strong sensation.](image2)
has taken place. This void can be either voluntary or involuntary (incontinence) depending on the circumstances. Urgency episodes are pathological and result in incontinence or small-volume voids, as well as a reduced intervoid interval. From the onset of the urgency episode to the void is an intrinsically short and inevitably variable time that is referred to as deferment or ‘warning time’ [11]. Similarly, the period between successive episodes of urgency can be measured (the refractory or urgency-free period; Fig. 3b). It is becoming apparent that the term ‘urge incontinence’ has been misleading and has hampered thinking in this area. We suggest that just as the term urge should in this context be replaced by the term (normal) desire to void, then logically the most accurate and comparable term should be ‘urgency incontinence’. Figure 3b is a suggested model of the effect of urgency on the micturition cycle that can generate testable hypotheses and hence advance understanding of OAB. With regard to this model, the following must be considered. What components are susceptible to intervention? Do all interventions (behavioural modification, pelvic floor contractions, biofeedback, electrical stimulation, antimuscarinic agents, drugs with other modes of action) act on this model in the same way? Will it be possible to prolong deferment time or will the goal of therapy be merely to prolong the refractory period or eliminate urgency altogether? Will this model help to define subsets of patients with OAB and give a greater insight into pathogenesis? Will it serve as a tool for determining prognosis?

THE URGENCY MODEL

Figure 4 shows a schematic to describe the symptomatic pathogenesis of OAB, assuming that fluid intake remains constant. The model is predicated on the theory that patients with OAB are abnormal because they experience urgency episodes; the flowchart explains how the other symptoms of OAB are secondary to the primary symptom of urgency.

Given that it is not possible to defer the void after an urgency episode, urgency results in an increased frequency of micturition. Another way of stating (and measuring) this is that the intervoid interval is reduced. If fluid intake remains constant, then fluid output also remains constant. Thus, increased frequency results in reduced volume voided per micturition. Incomplete bladder emptying with resultant residual volume may further contribute to a shortened intervoid interval. In Fig. 4 these steps, which are intuitive, logical and directly related to bladder function, are labelled as ‘1’. The other symptoms of OAB that also result from a reduced intervoid interval and are not so closely related to urgency are labelled ‘2’. Incontinence occurs in only a third of subjects with OAB [3] because leakage depends on a variety of urological and non-urological factors. For example, if the patient has good pelvic floor and urethral sphincter tone, the warning time may be long enough to allow a voluntary void; conversely, incontinence may occur because of sphincteric weakness. Other significant factors include the patient’s mobility, access to a toilet and other environmental factors [12]. In essence, the cause of incontinence is multifactorial and therefore its response to therapy more variable.

Nocturia is also common, but only a third of subjects with nocturia have OAB, the other causes being related to habit, drinking patterns, age, non-urological sleep
disturbances, cardiovascular problems and the use of certain drugs [13]. Thus, treatment of OAB will not necessarily have a consistent effect on nocturia episodes.

Urgency can reduce the intervoid interval, defined as the time between successive voids, which in turn presumably reduces the volume voided. The reduction in intervoid interval also contributes to incontinence and nocturia, although the relationship may be less obvious because these symptoms are multifactorial.

That urgency can lead to incontinence will train the patient to void more frequently; this in turn will exacerbate urgency, resulting in a vicious cycle of worsening OAB symptoms. The model suggests that this cycle may be broken by the effective initial treatment of urgency, a hypothesis that needs to be evaluated and tested in the clinical arena.

CURRENT TOOLS TO MEASURE URGENCY

SUBJECTIVE INSTRUMENTS

Currently, there are two subjective tools that have been designed to measure urgency, but neither accounts for the intervoid interval. Both of these tools seem to have significant flaws in their design and validation, as well as a lack of focus on the key symptom (i.e. urgency).

The Indevus Urgency Severity Scale (IUSS) is a 4-point qualitative scale that has been used to assess the severity of urgency in a clinical trial [14]. Inclusion criteria for patients in this study included ≥10 voids/day and ≥2 per hour. Patients were asked to rate the severity of ‘urgency’ before voiding on the following scale: 0, none; 1, mild, awareness of urgency but easily tolerated; 2, moderate, enough urgency that interferes with usual activities/tasks; 3, severe, extreme urgency/discomfort that abruptly stops all activities/tasks.

In this scale, categories 1 and 2 refer to urge and category 3 refers to urgency. This instrument measures a mixture of normal desire to void and urgency, and as such is both a qualitative and quantitative measure, but it fails to actually measure urgency alone. An attempt was made to provide psychometric validation of the IUSS [15], using patients with OAB and not on asymptomatic subjects.

The IUSS showed only low-to-moderate correlation with urinary frequency, frequency of urinary incontinence and Incontinence Impact Questionnaire scores. This might be expected, as an urgency score will not tightly correlate with symptom variables that have a multifactorial origin (Fig. 4). There was no correlation between the IUSS and average volume voided [16]. This is a serious flaw of the instrument, as an urgency measure should closely correlate with volume voided, as reduced bladder capacity will be a direct consequence of urgency (Fig. 4). Thus, the observations suggest that this instrument is not a robust measure of urgency. Indeed, in the reported clinical trial [14], the range of mean scores was narrow and low (1.77–1.55), suggesting that the IUSS was measuring normal desire to void rather than urgency.

The Urgency Perception Score (UPS), has been proposed as an instrument for assessing the perception of urgency in a recent clinical study [16]. Patients were asked to describe their typical response when they felt the desire to urinate. There were three possible responses to this question: (1) I am usually not able to hold urine; (2) I am usually able to hold urine until I reach the toilet if I go immediately; (3) I am usually able to finish what I am doing before going to the toilet. The UPS, quite correctly, purports to measure the perception of urgency rather than urgency per se. However, like the IUSS it has at least one category (response 3) that appears to be inconsistent with the compelling nature of urgency as defined by the ICS [6]. Similarly, response 1 would appear to be applicable to urgency with incontinence only. Inherent in the UPS is the conceptual assumption that normal desire to void (response 3), urgency (response 2) and incontinence (response 1) constitute a continuum of severity. While this idea is intuitively appealing, there has been no evidence to support such a progression. The UPS also lacks temporal characteristics that would enhance its ability to be understood by patients. For example, ‘I am not able to hold urine’ is not a clear statement in the absence of a specified period. Not being able to hold urine for 30 min is certainly different from not being able to hold urine for 3 h.

The psychometric variables of the UPS were validated using data collected in three clinical trials [17]. Construct validity was tested by correlation of the UPS and patient voiding-diary variables. Responsiveness and discriminant validity were assessed by ANOVA [17]. The UPS was found to be conceptually valid but to have uncertain responsiveness based on the few response options available to the patients [17]. In particular, a patient who says that he/she is usually able to finish a task before going to the toilet is given no room to improve, despite still having OAB. As such, the UPS tries to measure too many aspects of OAB and does not focus entirely on urgency. Consequently, its ability to measure urgency or its perception is limited.

One shortcoming of both subjective instruments is that they were not developed...
from patient perceptions of the key issues related to urinary urgency. Furthermore, as single-item scales, the measures cannot capture the broad impact of urgency and are unlikely to be as reliable or responsive to treatment-related change as a multi-item scale. Another weakness of the IUSS is that it does not appear to have been validated relative to the ideal anchoring instruments. The UPS has the additional disadvantage of having response choices that are not necessarily on the same conceptual continuum. Thus, neither the IUSS nor the UPS accurately measure the symptom of urgency, making their results inconclusive.

OBJECTIVE INSTRUMENTS

The ‘warning time’, defined as the ‘interval from first sensation of urgency to voiding’ as measured by a stopwatch, was proposed as a measure of urgency and used as the primary endpoint of a recent trial [11]. The authors noted that there was a large variation in the warning time of some individuals, and suggested that the median or minimum warning time might be more appropriate and relevant measures than mean warning time.

Although warning time is a potentially useful concept, this tool has not been validated to date. Also, the range of warning times (up to ~30 min in that study) suggests that the episodes measured were not ‘difficult to defer’. Indeed, it appears that ‘urge’ was considered synonymous with urgency. If the phraseology was changed from ‘difficult to defer’ to ‘cannot defer’, such measurement might become more reproducible. The converse of warning time may also be considered, i.e. the so-called ‘urgency free’ time or the refractory period between a void and the next onset of urgency (Fig. 3b). Further development work in this area is essential.

Patient-completed voiding diaries are commonly used as a primary tool for measuring symptoms in clinical trials of OAB. Diaries have been specifically used to record changes in the number of urgency episodes during the treatment of OAB in several recent trials [18–20]. The use of the patient-completed voiding diary for collecting both normative values of fluid intake and voiding variables in clinical trials is well accepted [21]. Recording urgency and other symptoms of OAB as variables in such diaries is less common and has received less validation. In a recent study, Brown et al. [22] examined the test–retest validity of a voiding diary specifically designed to assess symptoms of OAB, including urgency episodes, in a population of individuals who were receiving treatment for OAB or who had urge incontinence and were not receiving treatment for OAB. The test–retest reliability for OAB endpoints was acceptable, with intraclass correlation coefficients of 0.76–0.95 [22].

The convergent validity of urgency and incontinence episodes as recorded in the diary was shown by the significant correlation of diary endpoints with categorical responses to separate questions about these endpoints during the previous week [22]. The authors used interclass correlation coefficients as measures of reproducibility. They found that the measures of urgency episodes had equal or higher interclass correlation coefficients than those for urinary frequency and incontinence episodes. Thus they concluded that it was possible to measure urgency episodes in diaries. Further, they showed that a 3-day diary was as accurate as a 7-day diary for such measures [22].

CONCLUSIONS

The ICS has defined urgency as the primary symptom of OAB, noting it to be episodic and difficult to defer. This pathological state is in contrast to normal urge (desire) to void, which is easily suppressible and a part of normal bladder sensations that accompany filling. In this article, a hypothetical model is proposed suggesting that the relationship between urgency episode and warning (deferment) time results in a reduced interval. This cascade of events leads to the genesis of the other symptoms characteristic of OAB. Urgency can be measured quantitatively with voiding diaries, which are reliable and reproducible. Other existing subjective instruments for assessing urgency were reviewed and found to be inadequate, as they confuse the symptoms of ‘urge’ (normal desire to void) and urgency. There is obviously an essential need for any terminology to be clearly understood by both the patient and the doctor, considering the difficult and inherent limitations in being able to achieve this when dealing with a concept and symptom such as urgency. The model and observations presented here will hopefully generate scientific hypotheses that can be tested experimentally. This may in turn lead to a better understanding of the causes of OAB and hopefully more effective treatments.

CONFLICT OF INTEREST

All authors are consultants for Yamanouchi.

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Abbreviations: OAB(S), overactive bladder (syndrome); QoL, quality of life; IUSS, Indevus Urgency Severity Scale; UPS, Urgency Perception Score.
The Ibero-American experience with a re-adjustable minimally invasive sling

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OBJECTIVE
To report our experience with the Safyre™ (Promedon, Córdoba, Argentina), a new re-adjustable and minimally invasive sling for treating stress urinary incontinence (SUI), which combines the efficacy of slings with re-adjustability.

PATIENTS AND METHODS
In all, 126 consecutive patients with a clinical and urodynamic diagnosis of SUI had a Safyre sling procedure (mean age 63 years, range 40–71). Seventy-six patients (60%) presented after previous failed anti-incontinence procedures; all had a physical and clinical examination, a stress test, urodynamic study and assessment of pad use before the surgery. All the patients presented with symptoms of SUI and 37 (29%) also reported mild urgency.

RESULTS
The mean (range) follow-up was 18 (12–36) months, and the mean operative duration 25 min. Dystopia was repaired whenever necessary during the same procedure. The mean hospital stay was 24 h. In three implants (2%) the bladder was perforated. After surgery 26 patients (21%) developed urgency symptoms; during the follow-up 116 (92%) were continent, three (2%) reported an improvement and seven (6%) were dissatisfied.

CONCLUSION
The Safyre is a safe and quick procedure that allows for postoperative readjustment; this technique may be an attractive alternative if the good results obtained so far prove to be durable.

KEYWORDS
stress urinary incontinence, sling, female, failure, Safyre

INTRODUCTION
Pubovaginal slings date back to the beginning of the last century [1] and currently the sling technique has been considered to be the most effective for treating stress urinary incontinence [SUI] in patients with lesions of the intrinsic urethral mechanism [2]. However, morbidity and convalescence issues have stimulated the search for less-invasive procedures, e.g. minimally invasive slings and perirethral injections.

Synthetic tapes have been used and are very successful, giving strength to damaged tissues. An added benefit of synthetic slings is that they are placed using minimally invasive procedures, and thus reduce operative time, hospital stay and postoperative discomfort [3].

Since the marketing and success of the tension-free vaginal tape (TVT) technique, other products have been developed for suburethral slings. The self-anchoring Safyrem™ (Promedon, Córdoba, Argentina) sling has recently been added to the existing systems. This is a tension-free, synthetic sling, placed at the mid urethra so that urethral erosion is unlikely. It is a re-adjustable, self-anchoring synthetic sling that allows the tension to be re-adjusted after surgery should there be urinary leakage or retention [4]. According to the integral continence theory, the medial and distal thirds of the urethra are the most important. The Safyre system is based on this theory and on experimental studies of the female urethral closure mechanism [5].

Slings are now being used more frequently and the Safyre, which has incorporates new concepts, is an attractive alternative for the surgical treatment of SUI. We present our experience with this re-adjustable sling, focusing on the safety during and after surgery, and on efficacy in the medium-term of this procedure.

PATIENTS AND METHODS
In a prospective, multicentre, single-arm, unrandomized clinical study (approved by the Hospital Ethics Committee), from February 2001 to July 2002, 126 patients with SUI had a Safyre implant; in all there were 140 procedures (126 implants, six slings later tightened, four loosened and four removed). The mean (range) age of the patients was 63 (40–71) years.

All patients had a routine diagnosis for incontinence, including a history, an assessment of the effect on quality of life (Qol, based on the International Consultation on Incontinence Questionnaire, short form, ICQ-SF) [6], a gynaecological examination, a stress test, an assessment of pad use, and a urodynamic investigation. The last assessment used two urethral catheters (10 F for filling and 4 F for measuring bladder pressure), and a rectal 4 F catheter-balloon placed above the anal sphincter to measure abdominal pressure. The test included water cystometry, an assessment of Valsalva leak-point pressure with an intravesical volume of 200 mL and Valsalva manoeuvres, and a pressure-flow study.

The gynaecological examination showed mild cystocele in 62 patients (49%); 43 of the 62 (69%) were grade I and the rest grade II. A rectocoele grade I was diagnosed in 13 of the 126 patients (10%) and only symptomatic grade II cystoceles were repaired (three patients).
The stress test was positive in all patients, with a mean (range) leak-point pressure of 71 (38–90) cmH₂O in 54 (43%) and of 99 (91–125) cmH₂O in 72 (57%). Patients who had involuntary detrusor contractions during bladder filling or a maximum urinary flow rate of <15 mL/s and/or a postvoid residual urine (PVR) of >20% of the volume voided were excluded from the study, but those with irritative symptoms with no urodynamically confirmed involuntary contractions were included. Although urodynamically confirmed detrusor instability has no significant effect on surgical outcome, this decision was based on the concept of a postoperative improvement in sensory urgency, as described previously [7]. Patients with involuntary detrusor contractions were excluded from this initial study because of their less favourable prognosis for postoperative irritative symptoms [8]. Most patients (76, 60%) in the trial had at least one previously failed anti-incontinence procedure, the most common being anterior vaginal repair (Table 1).

Patients were followed at 1 month and then every 6 months, when the patients were questioned about the presence of spontaneous voiding, involuntary urinary leakage, bladder irritant symptoms and vaginal and suprapubic pain, followed by an assessment of QoL, a stress test and pad use.

The surgical results were classified according to Blaivas and Jacobs [9] into three categories: (a) cured, no incontinence; (b) improved, frequency of incontinence episodes less than once every 2 weeks; and (c) failure, frequency of incontinence episodes more than once a week.

The Safyre consists of a polypropylene mesh that acts as a urethral support, held between self-anchoring columns made of implant-grade polydimethylsiloxane polymer. These columns are the basis of the self-fixing system. To minimize surgical damage to the natural support structures of the pelvic floor a special 3.5 mm diameter needle allows both suprapubic and transvaginal approaches, according to the surgeon’s skills (Fig. 1). The versatile needle is assembled for the transvaginal approach when the hooked extremity is introduced inside the needle holder, and for suprapubic approach when assembled the other way.

The sling was placed with the patient in the lithotomy position under spinal anaesthesia; 2 g of cephalosporin were administered intravenously at the time of anaesthesia induction, followed by 1 g at 6, 12 and 18 h after the procedure. Two 0.5 cm transverse incisions are made close to the superior aspect of the pubic bone, 5 cm apart. A longitudinal vaginal incision 1.5 cm long is made, starting 0.5 cm from the urethral meatus. This incision is not allowed to encroach on the bladder neck. Dissection is used to create a 1-cm tunnel lateral to the urethra for introducing the Safyre insertion needle. First the needle is advanced through the vaginal tunnel until perforating the pelvic floor at the level of the mid-urethra. Then it is redirected against the back of pubic bone and advanced continuously to the benchmarks in the suprapubic area (transvaginal approach) (Fig. 2a). In the suprapubic approach the needle is advanced through one of the suprapubic incisions, down the posterior side of the pubic bone towards the vaginal incision (Fig. 2b). The needle tip remains in contact with the posterior pubic bone until it passes through the endopelvic fascia. Using the index finger of the other hand, the surgeon locates the tip of the needle and then guides it through the vaginal incision. Cystoscopy is

### TABLE 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (range) or N (%)</th>
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<tr>
<td>Previous procedure</td>
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<tr>
<td>None</td>
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</tr>
<tr>
<td>Anterior repair (Kelly plication)</td>
<td>37/76 (49)</td>
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<tr>
<td>Retropubic colposuspension</td>
<td>12/76 (16)</td>
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<td>Pubovaginal sling</td>
<td>12/76 (16)</td>
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<td>Periurethral injection</td>
<td>8/76 (11)</td>
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<td>Needle suspension</td>
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<td>Concomitant disease (diabetes, etc.)</td>
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</table>
used to exclude bladder perforation. After removing the holder, the Safyre is attached to the needle and pulled out to the suprapubic area. The same manoeuvres are repeated on the other side. The proper tension of the sling is adjusted, maintaining Metzenbaum scissors between the urethra and the sling, to prevent undue tension (Fig. 3). The extremities of the sling are cut and the Metzenbaum scissors removed. No further fixation is needed and the incisions are closed in the usual manner. An indwelling catheter is left in place overnight.

The procedure to tighten the Safyre can be done with the patient under local or spinal anaesthesia. As the extremities of the polydimethylsiloxane tails are easily palpable in the subcutaneous tissue, local anaesthesia with lidocaine 1% solution seems to be the method of choice. The sling arms are palpable and the patients can feel it for at least a year after surgery. However, in our experience, patients have not complained about this, even though they are asked. Usually, the readjustment of only one tail is enough, with no risk of significant deviation of the urethral axis. A small incision is made over the palpable tail extremity (close to the superior aspect of the pubic bone), and is gently dissected and pulled carefully until the proper tension is achieved (Fig. 4). Only the top incision need be opened to tighten the Safyre. During this manoeuvre Metzenbaum scissors should be maintained between the mesh and the urethra, to prevent over-correction. The bladder is filled with saline solution before the procedure, so the patient can be asked to cough and to repeat Valsalva manoeuvres to check for leakage. Generally, any readjustment is proposed within 30 days of the original surgery, but theoretically it can be done at any time after surgery because of the formation of a fibroblastic pseudocapsule surrounding the polydimethylsiloxane tail of the Safyre that permits easy dissection and mobilization of the tails inside this pseudocapsule whenever necessary.

The procedure to loosen the Safyre is best done under spinal, intravenous or local anaesthesia. When local anaesthesia is used, both the suprapubic area (including the urethropelvic fascia) and anterior vaginal wall (including the rectus muscle and fascia) must be anaesthetized with lidocaine 1% solution. It is not necessary to make a suprapubic incision to reach the sling; only the bottom incision should be opened. However, it is necessary to anaesthetise the urethropelvic fascia to avoid pain while mobilizing the tails. A longitudinal vaginal incision 1.5 cm long is made, starting 1 cm from the urethral meatus, and the polypropylene mesh dissected from the urethropelvic fascia. The tails are dissected bilaterally, grasped with haemostatic clamps and pulled back, until Metzenbaum scissors or a right-angle clamp can be interposed between the mesh and the urethra, to prevent undue tension and to check whether the space between the mesh and the urethra is enough to avoid urethral obstruction. A Foley catheter is left in place overnight. The procedures to tighten or loosen the Safyre are easy and take ≈20 min. No complications were identified during either procedure.

RESULTS

The basic characteristics and the demographic data of all patients are shown in Table 1. The mean (range) follow-up period was 18 (12–36) months, the duration of surgery 25 min and the hospitalization 24 (12–36) h. All patients went home the day after the surgery. The overall complication rate was 33% (42 patients); most of these women had more than one complication. Peroperative complications occurred in three women (2%), with perforation of the upper lateral wall of the bladder in all three. All three patients had had at least one previous surgical procedure for SUI; the Foley catheter was kept for 48 h in these patients and they developed no further complications. There was no bleeding, blood transfusion, urethral or vaginal perforation during the procedure in any patient.

Urinary retention was diagnosed when the residual volume, obtained by urethral catheterization after voiding, was >100 mL. Patients who could not void spontaneously immediately after surgery were maintained on clean intermittent catheterization for 4 weeks, when the Safyre was loosened if the retention persisted. All patients voiding spontaneously soon after surgery had a PVR of <100 mL and were thus considered to have no retention. Following these criteria there was urinary retention in four of the 126 patients (3%) who could not void spontaneously 4 weeks after surgery. All had the sling tension loosened under local anaesthesia and voided spontaneously, with completed relief of irritative symptoms and with a mean PVR of 60 mL (after the tape did not need to be sectioned in any patient.

The main complication after surgery was ‘de novo’ urgency, which occurred in 26 patients (21%); this symptom occurred immediately after surgery and no specific treatment was used. The symptoms resolved in all patients within 4 weeks. Of the 37 women (29%) with urgency before surgery, none, seven (19%) and 30 (81%) reported being worse, unchanged or improved, and of the 89 who had more than one complication. Peroperative complications occurred in three women (2%), with perforation of the upper lateral wall of the bladder in all three. The overall complication rate was 33% (42 patients); most of these women had more than one complication. The symptoms resolved in all patients within 4 weeks, when the Safyre was loosened if the retention persisted. All patients voiding spontaneously soon after surgery had a PVR of <100 mL and were thus considered to have no retention. Following these criteria there was urinary retention in four of the 126 patients (3%) who could not void spontaneously 4 weeks after surgery. All had the sling tension loosened under local anaesthesia and voided spontaneously, with completed relief of irritative symptoms and with a mean PVR of 60 mL. After the tape did not need to be sectioned in any patient.

Six patients (5%) presented with vaginal erosion of the tape. They had vaginal pain, discharge and bleeding, dyspareunia, and dysuria, and one had recurrent UTIs. On physical examination the erosion of Safyre was clearly visible. They were unsuccessfully treated with topical ointments and oral antibiotics. All of them underwent
transvaginal tissue debridement. The protruding part of the tape was removed in four women and the tape was covered by an advanced vaginal flap in the others. These patients were then followed; all remained continent and a vaginal examination showed no visible or palpable abnormality.

Six patients (5%) had the tape re-adjusted later to tighten the Safyre; they presented with urinary incontinence after the initial surgery and the tape was re-adjusted so they could be continent. The results were good in four patients (cure of preoperative complaints) and improved in two.

According to the Biaivas and Jacobs criteria [9] after the 18-month mean follow-up, 116 of the 126 patients (92%) were continent, three (2%) reported a significant improvement and seven (6%) were dissatisfied with the procedure and considered as failures. The ICOQ-SF showed significantly better scores on all questions than before surgery (80% of patients reported that they had fewer urinary symptoms after surgery). At the end of the follow-up the stress test was negative in all the continent and incontinent patients, and the incontinent group was using, at most, one perineal pad daily.

DISCUSSION

Recent studies agree that pubovaginal slings and retropubic urethrocystopexy are the best techniques for resolving SUI during a long-term follow-up [10]. However, sling procedures require a considerable period of surgical training, the inconvenience of needing a donor site to obtain the fascia to be used in the surgery, and risks of infravesical obstruction and other bladder dysfunctions [9]. Retropubic urethrocystopexy requires an abdominal incision, with increased morbidity and hospitalization, high costs when performed using laparoscopic access, and considerable training and experience [5]. Therefore, all efforts in developing minimally invasive techniques are justifiable.

Conceptually the Safyre corresponds to a sling but creating a suburethral support zone increases urethral resistance, and consequently the rotational and descending movement of the urethra is avoided when abdominal pressure increases. Additionally, it facilitates the coaptation of the urethral lumen at rest and under stress. However, contrary to the classical pubovaginal slings, the Safyre is applied to the medial third of the urethra, where the pubourethral ligaments responsible for the natural stability of the urethra are inserted [11]. Maintaining the sling in the appropriate position is explained by the salients and re-entries, creating a hook-like effect on the pelvic fascia and the abdominal smooth muscle, as well as by local inflammatory reactions.

The Safyre insertion is tension-free and not restricted by the size of the bladder neck, as in conventional slings. Although 3% of the present patients had urinary retention after surgery, the Safyre allowed the tension to be readjusted with no difficulties, and under local anaesthesia; the patients voided spontaneously with complete relief of irritative symptoms and a mean PVR of 60 mL. Although there was no urodynamic evaluation after surgery we assume that this technique does not alter voiding pressure, as happens with periurethral injections. Both the Safyre and TVT are applied with no tension and do not limit bladder neck opening, as do conventional slings.

The present results confirm the feasibility and safety of the Safyre for SUI. Since the first report by Ulmsten et al. [12], the TVT has become a popular method for genuine SUI. A recent review of 11 studies with objective endpoints gave a cure rate of 87% at a mean of 17 months after surgery [13]. Our group has experience with TVT in 110 patients [14]; the mean follow-up was 18 months and the main complication was irritative voiding symptoms, reported by 29% of patients soon after surgery (up to 4 weeks). These patients had a new urodynamic evaluation, which showed detrusor instability in 30%, urinary incontinence in 30% and no significant changes in the remainder. The frequency of these symptoms was similar to those with the Safyre method. De novo urge symptoms may be related to changes in para-urethral collagen metabolism and fibrosis around the tape. Interestingly, in the Safyre group urge symptom rates did not differ with menopausal status. The safety is comparable with TVT and Safyre in our experience, but the Safyre was more effective than TVT (92% vs 81%), possibly because the Safyre can be readjusted if there is urinary leakage. The infection and erosion rates were similar for TVT and Safyre in our experience. The present study was conducted in a public academic centre where there are urologists in training, and thus the higher rates of tape erosion might be a result of excessive manipulation of the tape and longer operation times. All tape infections were early in the experience with the Safyre (the first 20 cases). Currently care is taken to ensure that there is adequate vaginal-incision suturing, a quicker operation and that manipulating the tape is minimized.

Although we did not compare the Safyre directly with other minimally invasive techniques, there are specific and significant differences in the biochemical and biomechanical properties of this device. As opposed to TVT or other polypropylene-based minimally invasive slings, the smooth surface of Safyre mesh allows for easy primary adjustment during the implant, and even during eventual readjustment, besides keeping its resistance and shape because of its low deformity rate. Moreover, the elasticity of the polydimethylsiloxane tails allows fine movements according to changes in the patient’s abdominal pressure, acting as a dynamic support. Furthermore, the Safyre self-anchoring system is unique in allowing readjustment after surgery. The procedure is minimally invasive and no large abdominal incision is required for harvesting fascia, or to fix the sling to the aponeurosis of the abdominal rectus muscle, as in a classical sling. The sling tension can be re-adjusted in patients with persistent incontinence or urinary retention, avoiding major surgery such as urethrolysis or the need for another sling insertion, thus reducing costs; this procedure is a promising step forward in the surgical treatment of SUI.

CONFLICT OF INTEREST

None declared.

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Abbreviations: SUI, stress urinary incontinence; TVT, tension-free vaginal tape; QoL, quality of life; ICIQ–SF, International Consultation on Incontinence Questionnaire, short form; PVR, postvoid residual urine volume.
Effects on sleep of anticholinergics used for overactive bladder treatment in healthy volunteers aged ≥50 years

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OBJECTIVE
To study the influence of oxybutynin, tolterodine or trospium chloride, anticholinergics used to treat bladder overactivity, on sleep and the cognitive skills of healthy volunteers aged ≥50 years.

RESULTS
There was a significant reduction in rapid-eye movement (REM) sleep of ≥15% and a slightly (but not significantly) greater REM latency after oxybutynin and tolterodine than with placebo. After trospium chloride, REM duration and latency were comparable with placebo. There was no effect of the tested anticholinergics on cognitive subjective sleep variables.

CONCLUSION
Individuals aged ≥50 years had a more distinct impairment of REM sleep after oxybutynin and tolterodine than had young people, but the reduction in REM sleep did not reach a pathological degree in this single-dose study. There was no apparent impairment of concentration or cognitive function, but impairment of cognitive function and neuropsychological side-effects cannot be excluded, especially when elderly patients with impaired REM sleep from various psychiatric diseases (e.g. depression) and/or sleep disturbances are given oxybutynin or tolterodine in long-term treatment.

KEYWORDS
oxybutynin, tolterodine, trospium, anticholinergics, sleep, cognitive function

INTRODUCTION
Anticholinergic drugs, e.g. oxybutynin, tolterodine and trospium chloride, are used for treating overactive bladder symptoms that predominantly occur in elderly people [1,2]. Some of these drugs have substance-specific side-effects on the CNS [3]. Oxybutynin causes cognitive impairment [4–6], changes in CNS electrical activity [7], psychosis, hallucination, confusion, impaired concentration and orientation [8,9], as well as drowsiness and disturbed sleep [10]. Tolterodine leads to dizziness, sleepiness and nervousness [11,12], and recent case-reports have described memory impairment [13,14] and hallucinations [13]. No such side-effects have been reported with trospium chloride.

These differences are a result of drug-specific pharmacodynamic and pharmacokinetic properties, e.g. quaternary amines, like trospium, do not readily cross the blood–brain barrier, whereas tertiary amines [15,16] like oxybutynin and tolterodine do. We recently investigated the influence of trospium chloride, oxybutynin and tolterodine on the structure and quality of sleep in young healthy volunteers [17]. In that study there was a significant reduction in the duration of rapid-eye movement (REM) sleep, and an increase in stage 1 sleep and in REM latency after oxybutynin. However, young people are not the main target patients for anticholinergic drugs. The pharmacokinetics and pharmacodynamics of these substances might change with age [8], leaving the elderly more susceptible to CNS side-effects [4]. Thus, in the present investigation we studied the influence of single doses of different anticholinergics on sleep and cognitive skills of healthy volunteers aged ≥50 years.

SUBJECTS AND METHODS
A randomized, double-blind, placebo-controlled study was conducted in a crossover design identical to that of the previously study in healthy young volunteers [17]. After initial polysomnography and a thorough examination, 25 volunteers were included in the study, 24 of whom (12 men and 12 women, mean age 60 years, SD 3, range 51–65) completed it (one withdrew). The exclusion criteria were sleep disturbances and organic or psychiatric diseases which influence sleep, or which were contraindications to one of the study medications. The study was approved by the local ethics committee of the Charité Universitätsmedizin Berlin.

Volunteers underwent four 2-night periods of polysomnography in a sleep laboratory, with the study periods separated by a 12-day ‘washout’. On the first night of each period, volunteers were allowed to adapt to the study situation, and study medications were administered on the second night as one dose containing 45 mg trospium chloride (Spasmex®, Dr R. Pfleger GmbH, Germany), or 4 mg tolterodine (Detrusitol, Pharmacia GmbH, Germany), or 15 mg oxybutynin (Dridase, Sanofi-Synthelabo GmbH, Germany), or placebo, 2 h before polysomnography started. Participants were randomly assigned to one of the four treatment sequences using the Latin square technique.

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Sleep stages were scored visually according to the standard procedure [18]. REM duration, as a percentage of total sleep time (TST), was chosen as the primary variable and tested for overall differences using Friedman’s two-way nonparametric ANOVA. All objective and subjective sleep variables, as well as variables of psychometric testing, were analysed using the Wilcoxon matched-pairs signed-ranks test. All tests except that used for the primary variables had to be interpreted exploratively.

To assess subjective quality of sleep, volunteers completed the structured questionnaire of the German Society of Sleep Medicine, in the evenings and mornings of polysomnographic recording. Potential impairment of cognitive function was assessed 1 h after administration of the study medication, using a number-combination test (Der Zahlen-Verbindungs-Test, ZVT) for evaluating information-processing capacity and working velocity [19], and the d2 test of attention for assessing individual sustained attention and concentration [20].

RESULTS

The duration of REM as a percentage of sleep duration was significantly different (P = 0.007) among the four treatment groups (Table 1). Further analyses revealed reductions in the median REM sleep duration of 14% after oxybutynin (P = 0.002) and of 15% after tolterodine (P = 0.012) compared with placebo; the duration of REM after trospium chloride was not significantly different from placebo.

A second exploratory analysis showed an insignificant (P = 0.074) prolongation of REM latency (the time between sleep onset and the first period of REM) after taking oxybutynin and tolterodine, compared with placebo and trospium chloride (Table 1). There were no significant changes for the other secondary objective variables, i.e. duration of various sleep stages (stage 1, stage 2, slow-wave sleep; SWS) as a percentage of TST, sleep latencies (sleep onset latency, SWS latency), and sleep efficiency (Table 1). Subjective sleep variables showed no statistically significant change. Sleep duration and quality, and morning feeling and day efficiency, were not affected by the different medications.

None of the study medications influenced the cognitive skills of the volunteers (Table 1); there were no significant changes in vital signs, electrocardiogram and laboratory variables. In all, 61 adverse events were recorded; all were assessed as mild or moderate. There were differences among study medications only for the adverse event of dry mouth [placebo, three; trospium chloride, five; tolterodine, four; and oxybutynin eight].

DISCUSSION

The incidence and intensity of CNS side-effects of anticholinergic drugs depend on the pharmacokinetic and pharmacodynamic properties of the agents, and can be more pronounced in the elderly, even if the dosage is adjusted to account for age-related changes in body composition and drug elimination [3]. Several authors have shown relevant neuropsychological side-effects in elderly patients treated with the tertiary anticholinergics oxybutynin [8,9] and tolterodine [11–14]. These side-effects did not occur after treatment with trospium chloride, a quaternary anticholinergic. Furthermore, sleep disturbances were reported with oxybutynin [10]. Changes in sleep structure are mainly related to REM sleep and manifest themselves in an increased REM latency and a reduced REM duration [17,21–24]. In the earlier investigation [17] oxybutynin had most influence on sleep structure, as reflected by REM suppression and mild sedation, while subjective variables and psychometric tests remained unaffected. The clinical impact of these effects was rather small in healthy young people.
The present study was conducted to verify these results for the main target population for these drugs, individuals aged ≥50 years. Using the same study design as in the previous study (randomized, double-blind, placebo-controlled, crossover design), objective and subjective variables of sleep structure and cognitive function were studied as indicators of CNS effects. The crossover design was chosen to minimize the influence of inter-individual variance of sleep variables. Study medications were given as a single dose containing the total recommended daily dose (oxybutynin 3 × 5 mg, tolterodine 2 × 2 mg, trospium chloride 3 × 15 mg) to shorten the treatment period. Previous studies showed that this procedure is suitable for detecting changes in neurobiological activity [7,17,25]. The duration of REM sleep was used as the primary target variable because it reflects the night as a whole, so that compounds with different pharmacokinetic properties can be compared.

In the present study there was a reduction in REM sleep =15% after oxybutynin and tolterodine; in a previous study with young volunteers the reduction was =8% after oxybutynin and 5% after tolterodine, which was not statistically significant [17]. In the older subjects, REM latency was slightly (but not significantly) increased after oxybutynin and tolterodine compared to placebo. However, after trospium chloride, REM duration and latency were similar to that with placebo in both studies. Hence, individuals aged ≥50 years had a more distinct impairment of REM sleep after oxybutynin and tolterodine than had younger people. However, as the reduction in REM sleep did not reach a pathological degree, an impairment of concentration or cognitive function was not to be expected. There was no apparent effect of the tested anticholinergics on cognitive and subjective sleep variables after one dose in the present subjects, but an impairment of cognitive function and neuropsychological side-effects cannot be excluded, especially when elderly patients with REM sleep impaired by various psychiatric diseases (e.g. depression), and/or sleep disturbances [26], are treated with oxybutynin or tolterodine. Therefore, we propose modifying the previously published recommendation to discontinue anticholinergics in patients with neuropsychological side-effects [13], and suggest that, for these patients, a change to trospium chloride should be considered before anticholinergic treatment is abandoned. Nevertheless, the present study investigated the effects of the three anticholinergics in single doses approximating the total usual daily dose, and these drugs are often used in chronic diseases. Thus, it is still unknown how effects on sleep structure develop in the long term and how these effects influence cognitive skills.

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CONFLICT OF INTEREST

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Abbreviations: REM, rapid eye movement; TST, total sleep time; SWS, slow wave sleep; ZVT, Der Zahlen-Verbindungs-Test.
Urethral stents for detrusor sphincter dyssynergia

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INTRODUCTION

In the USA alone, over 10 000 traumatic spinal cord injuries occur each year, predominantly affecting men aged 20–40 years [1]. Spinal cord injury can also result from myelopathy, myelitis, arachnoiditis, vascular disease or arteriovenous malformations. In patients with suprasacral, subpontine lesions the typical neurogenic bladder behaviour is involuntary external sphincter contraction occurring simultaneously with hyper-reflexic detrusor contractions. This detrusor–sphincter dyssynergia (DSD) results in dangerously high intravesical pressures that pose significant risks for the upper tracts, and complications such as pyelonephritis, calculus formation, sepsis and renal decompensation occur in more than half of patients if not treated. The current management of DSD involves reducing intravesical pressures with antimuscarinic medication, and minimizing intravesical volumes by clean-intermittent catheterization (CIC). This may not be feasible in quadriplegics who lack manual dexterity or in patients who do not co-operate with the catheter regimen. In such cases, an indwelling catheter can ensure drainage, but this is limited by the almost inevitable development of urethral erosion (with a urethral catheter), chronic infection, squamous metaplasia and calculus formation.

The results of the medical management of DSD have been consistently disappointing; centrally acting muscle relaxants are ineffective, and peripherally acting agents are associated with toxicity. External sphincterotomy was first introduced by Watkins in 1936 for reducing outlet resistance, and to provide low-pressure drainage. Despite initial enthusiasm, sphincterotomy has been hampered by failure to fully eliminate residual urine, the potential for significant haemorrhage and the need to repeat the procedure in up to 25% of patients [2]. Patients are also reliant upon condom-catheter drainage and less than half of patients continue with this drainage method in the long term. An alternative, less-invasive method is sphincter ablation by direct injection of Botulinum toxin. This provides only temporary relief, and repeat injections are necessary every couple of months. Balloon dilatation is another alternative, but this is restricted by recurrent obstruction and excessive bleeding [3].

Given the difficulties in establishing low-pressure bladder emptying in these patients, therapeutic innovations continue to be introduced. Intraurethral stent placement was introduced by Fabian in 1980 [4] as an alternative to long-term indwelling urethral catheterization, and intraurethral stents have since become recognized as a minimally invasive, effective treatment option for urethral strictures and prostatic obstruction. The attractive features of an indwelling stent are its potential reversibility and provision of a wide lumen, which facilitates both urinary drainage and instrumentation. The disadvantages include biocompatibility concerns, hyperplastic reactions, encrustation, infection and calculus formation [5]. The application of intraurethral stents in the management of DSD has been investigated in several studies in the last decade, and these are reviewed here.

There are two types of urethral stents, permanent or temporary; the latter have become popular in managing prostatic obstruction and urethral strictures, but clinical experience in managing DSD with these stents is limited. To date, the most extensive clinical experience reported in this area has been with the Urolume™ permanent stent (American Medical systems, Minnetonka, MN; also known as the Wallstent™ in Europe, Medinvent SA, Lausanne, Switzerland).

PERMANENT STENTS

The Urolume stent was developed as a self-expanding endoprosthesis to maintain the patency of stenotic arteries after balloon angioplasty. In 1988, Milroy et al. [6] first described its use in managing bulbar urethral strictures. The stent is a braided, pliable, self-expanding cylindrical mesh of corrosion-resistant, nonmagnetic super-alloy wire (Fig. 1). The radial mesh design exerts a strong, continuous, outward radial force against the urethral lumen to maintain patency of up to 42 F (14 mm diameter).

The first report on the effectiveness of urethral stents for treating DSD was by Shaw et al. in 1990 [7], using the Urolume stent. Since then several studies have confirmed the value of stent placement in this clinical scenario. Noll et al. [8] reported that, in 22 of 24 men with severe DSD, infravesical obstruction was relieved by the Wallstent. Most of these patients (71%) had previously had an unsuccessful surgical external sphincterotomy. McInerney et al. [9] used the Wallstent in 22 men with DSD; half of these had previously had repeated unsuccessful external sphincterotomy, and three had artificial urinary sphincters in situ. After stent placement, 15 men (68%) had effective urinary drainage, and three (14%) developed bladder neck obstruction. None of the men with artificial urinary sphincters drained adequately after stent placement.

In 1993, Chancellor et al. [10] reported their experience with the Urolume stent in 25 men with spinal cord injury and DSD. At 1 year after insertion voiding pressures and residual urine volumes remained low, and bladder capacity was unchanged. The stent migrated in three (12%) men and one man developed pyelonephritis. The authors concluded that this simple technique is an attractive alternative to formal surgical sphincterotomy.

In 1994, Rivas et al. [11] compared Urolume implantation with surgical external sphincterotomy in 46 men with spinal cord injury and DSD over a follow-up of...
were maintained at 5 years of follow-up, and in 6.9%. Significant reductions in mean used in 52% of patients, two in 30% and three external sphincter coverage; one stent was about a third of patients required at least two previous history of external sphincterotomy. The North American Multicentre Urolume Trial has follow-up of 160 patients in 15 centres in the over a follow-up of 2–33 months [3]. A 5-year clinical study of the Urolume intervention. The first large clinical study of the Urolume stenting is an effective, potentially operative success was 94% at 1 year and 98% at 5 years. The authors concluded that, overall, stent placement was as effective as traditional sphincterotomy, but preferable because of the shorter hospital stay and potential reversibility. The results of Urolume removal have been reported by members of the North American Study Group [18]; the stent is removed by endoscopically grasping several rows of the prosthesis wire at least 2 mm from the distal end of the stent. Gentle withdrawal permits stent elongation and narrowing, facilitating intact removal. Failure to remove the stent intact might occur if too few wires are grasped initially, in which case piecemeal retrieval of the individual wires is required. If stent epithelialization is evident, preliminary endoscopic tissue resection is necessary, using low, brief, pure-current settings to avoid thermal disruption of the wire components. Twenty-one patients (13%) required stent removal at the time of initial insertion, mainly because of misplacement or migration. Retrieval was easy, and a stent was then correctly placed in 90% of the patients. In the longer term, stent removal was necessary in 31 (20%) of the overall study group at a mean of 22 months after placement, most stents being removed at 2–4 years because of stent migration. Less common indications for removal included inadequate epithelialization, UTI, pain and squamous metaplasia. Thirty of these patients (97%) had their stents removed successfully and six (4%) had the stent replaced successfully. About half of the stents were removed intact and half removed piecemeal, and open removal was necessary in one patient. The degree of urothelial trauma caused by stent removal was reportedly minimal, although more marked for piecemeal removal. There were no lasting consequences of stent removal, showing the potential reversibility of these stents.

The first large clinical study of the Urolume was the North American multicentre trial, which prospectively investigated the efficacy in 153 men with spinal cord injury and DSD over a follow-up of 2–33 months [3]. A 5-year follow-up of 160 patients in 15 centres in the North American Multicentre Urolume Trial has since been published [15]. The overall results of these two studies were unaffected by a previous history of external sphincterotomy. About a third of patients required at least two insertion procedures to achieve adequate external sphincter coverage; one stent was used in 52% of patients, two in 30% and three in 6.9%. Significant reductions in mean voiding pressure and residual urine volumes were maintained at 5 years of follow-up, and bladder capacities remained unchanged. However, despite these significant reductions in residual urine volume, the absolute volumes were still high throughout the follow-up, at a mean of 132 mL at 5 years. Of 115 (72%) patients with autonomic dysreflexia before the study, this remained resolved in 70% at 1 year, and improvement was maintained at 5 years. Sixty-three of 86 patients (85%) who required an indwelling urinary catheter before surgery remained converted to condom-catheter drainage. Before surgery, hydronephrosis was present in 16% of 320 renal units in 160 patients, and this reduced to 4% of units at 1–5 years. Data on colonization and infection rates were unavailable for before and soon after surgery; for the remainder of the study, asymptomatic bacteriuria was present in >90% of patients, but only 3–12% had a symptomatic UTI. Erectile function and antegrade ejaculation remained unaffected by stent placement for the duration of the study. On cystoscopy of the implant site, epithelialization began at 3 months and complete urethelial stent coverage increased from 49% of patients at 1 year to 96% at 5 years. At 1 year 20% of patients had a moderate-to-severe intraluminal hyperplastic response, as had 7% at 5 years. Intra-stent stenosis developed in only 3% of patients, encrustation in 6% and there was no calculus formation. Stents were removed in 24 patients (15%), primarily because of stent migration, and four of these subsequently had a further stent placed successfully. Although there was no significant bleeding or soft-tissue erosion, 47 patients (26%) developed bladder neck obstruction, of whom less than half required surgical incision. Subjective improvement in bladder emptying was reported by 91% of patients at 1 year and by 74% at 5 years, whilst the physician’s subjective perception of operative success was 94% at 1 year and 98% at 5 years. The authors concluded that Urolume stenting is an effective, potentially reversible alternative to surgical external sphincter destruction.

Sauerwein et al. [16] also reported improved urodynamic, radiological and clinical findings in 51 men with spinal cord injury and DSD at up to 3 years of follow-up. Chancellor et al. [17] compared the results of Urolume placement with external sphincterotomy in a multicentre randomized trial. Urodynamic data, voiding questionnaires and quality-of-life measurements were analysed over 2 years. There was a significant reduction in maximum detrusor pressures after both procedures, but reductions in residual urine volumes after stent placement were only significant at 3 months, whereas sphincterotomy continued to minimize postvoid residual volumes at 2 years. Bladder capacity was unaffected by either procedure. Postoperative bleeding was insignificant in both groups and the hospital stay was generally shorter for stented patients. A significant improvement in bladder emptying was reported more often by patients with stents, but patients who had undergone sphincterotomy tended to report less worry, bother, hampering of daily activities and interference with social activities. The authors concluded that, overall, stent placement was as effective as traditional sphincterotomy, but preferable because of the shorter hospital stay and potential reversibility.

The treatments were equally effective in reducing voiding pressures and residual urine volumes, without adversely affecting bladder capacity and with similar surgical complication rates. However, stent placement was less expensive, was associated with less bleeding, and had a significantly shorter operating time and hospital stay. Similar conclusions were reported by Chancellor et al. [12] when they prospectively compared stent placement, external sphincter balloon dilatation and traditional surgical external sphincterotomy in 61 patients. Juma et al. [13] highlighted the simplicity of stent insertion, the short hospital stay and low short-term morbidity in their cohort study of 10 patients. In 1996, McFarlane et al. [14] reported the results of Urolume implantation in 12 patients with a 5-year clinical follow-up, which included urodynamic and ultrasonographic studies. Although stent migration, erosion or infection did not occur in that study, stent removal was necessary in two patients and half developed bladder neck obstruction which required surgical intervention.

FIG. 1. The Urolume permanent urethral stent.
A further long-term result by Hamid et al. [19] showed a favourable urodynamic outcome at a mean follow-up of 12 years in seven of 12 patients with DSD. The main complication was bladder neck dysynergia, successfully managed by bladder neck incision.

**TEMPORARY STENTS**

Permanent stents might cause problems if epithelialization is poor, or if a hyperplastic response leads to urethral occlusion; concern about the potential long-term risk of malignancy remains. To circumvent these difficulties, some authors have investigated the Memokath™ temporary urethral stent (Engineers & Doctors A/S, Hornbaek, Denmark; Fig. 2).

Vaidyanathan et al. [20] reported long-term results for 10 men with spinal cord injury and urinary retention. Although the initial results were good, nine required stent removal because of a hyperplastic response leading to occlusion, recurrent UTI, frequent episodes of autonomic dysreflexia and migration related to manual bowel evacuation. They advocated the stent only as a temporary measure in selected patients with no history of UTI and need for manual bowel evacuation. A single-centre 7-year experience was reported by Hamid et al. [21] in 25 patients with DSD. Urodynamically, there were significant reductions in maximum detrusor pressures, duration of contraction and residual urine volume at 6 months after stent insertion in 23 patients. Nineteen patients (83%) required stent removal at a mean of 20 months for various reasons, including autonomic dysreflexia, stent migration, encrustation, incomplete bladder emptying, and entrance to a fertility programme. Stent removal was easy within 2–3 min, with minimal urethral trauma. The authors concluded that this procedure was safe, easy to perform, and well suited as a temporary and reversible measure for patients with the potential to recover manual dexterity to use CIC or who wished to enter a fertility programme.

As an alternative to formal external sphincterotomy, Low et al. [22] implanted 26 Memokath stents in 24 high tetraplegic males with DSD who were unable to catheterize. Disappointingly, implantation failed to improve bladder emptying and 19 patients (79%) required stent removal because of infection or stent migration.

The Memotherm™ stent (Angiomed, Karlsruhe, Germany) was originally developed as a permanent stent for the relief of benign prostatic obstruction, but has since been modified to become an essentially temporary stent. This flexible wire mesh is composed of the thermo-reactive material Nitinol, which has its maximum expansion force at 37 °C; this heat-sensitivity allows repositioning. Garcia et al. [23] implanted the Memotherm stent in 24 spinal cord injured patients with DSD. Over a mean follow-up of 15 months, bladder leak-point pressures and residual urine volumes remained significantly low. The stent migrated in four patients, and two developed infection and calculus formation, necessitating stent removal.

**CONCLUSIONS**

The introduction of urethral stenting as a treatment for DSD in males with spinal cord injury represents a significant advance in urological practice. The various studies cited show that stenting is as effective as sphincterotomy. The advantages of sphincter stenting include ease of placement, which if performed correctly is associated with minimal complications and a short hospital stay. However, residual urine is not eliminated by sphincter stenting, and although the values reported are an improvement on those before stenting, the volumes remain considerable. This could be explained by 25–50% of patients developing significant bladder neck obstruction secondary to a hyperplastic tissue response. To date, the published reports remain unclear on this matter. It has been suggested that Urolume stent insertion is potentially reversible, but most Urolume stents are virtually completely epithelialized as early as 6 months after placement, which would be expected to render removal difficult. Stent removal was necessary in 20% of the large group of patients in the North American Multicentre study, and only half were removed intact. In our experience, stent removal can be difficult and time-consuming, and attention has been drawn to this by Wilson et al. [24]. Only 4% of patients have had a stent reimplanted successfully after removal, further indicating that stent placement should not be considered a procedure that is easily revised.

Overall, placing a permanent sphincter stent such as the Urolume is no better than traditional sphincterotomy, merely equally effective. Although considerable experience has been gained with the use of the Urolume stent, placing this stent must still be regarded as being only potentially reversible, as the ease and safety of stent removal remain undetermined. Thus temporary stents appear to be attractive because they are easily removable, particularly if patient indecision or concerns about fertility are major management issues. However, to date the clinical experience with temporary stents is limited.

The ‘gold standard’ of managing DSD after spinal cord injury remains the combination of an effective CIC regimen (by patient or carer), together with antimuscarinic pharmacotherapy. In the authors’ experience, most patients are able to co-operate with such an approach, and alternative methods are only required for a few. For these, apart from stent implantation, current options include an indwelling catheter, preferably via the suprapubic route (reversible), external sphincterotomy (irreversible), augmentation cystoplasty (irreversible) and incontinent ileovesicostomy (irreversible). Stent placement would appear to be a suitable, but only potentially reversible, alternative to the equally effective but irreversible external sphincterotomy, and should only be considered if the patient does not agree to the above alternatives.

**CONFLICT OF INTEREST**

None declared.
URETHRAL STENTS FOR DETRUSOR SPHINCTER DYSSYNERGIA

REFERENCES


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Abbreviations: DSD, detrusor-sphincter dyssynergia; CIC, clean-intermittent catheterization.
Tamsulosin in the management of patients in acute urinary retention from benign prostatic hyperplasia

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INTRODUCTION

BPH is common in men aged >40 years; the incidence and prevalence increase with age, and 30% of men aged >70 years have symptoms related to prostatic enlargement [1]. These symptoms impair physiological and functional well-being, and interfere with daily living [2]. Although BPH rarely threatens life, it can contribute to acute urological complications, particularly acute urinary retention (AUR), which is often considered to be the most serious complication of BPH [3]. AUR is relatively common, painful and distressing for the patient, and has considerable economic costs [4]. Early estimates of incidence varied widely, but better estimates now available from population-based studies of men in the community [5] indicate an incidence of 5–25 per 1000 person-years, or 0.5–2.5% per year. The risk is cumulative and increases with age.

AUR is one of the main indications for TURP, reported as the precipitating reason for 25–30% of emergency procedures [6,7]. After an episode of spontaneous AUR (i.e. not caused by a specific event such as surgery, catheterization or drug), 15% of patients in one long-term study had another episode of AUR, and 75% had subsequent surgery [8].

The current management of AUR is to insert a urinary catheter to relieve symptoms, but this can add to the patient’s symptoms if UTI develops. In addition to being uncomfortable for the patient, this is an avoidable risk factor for blood loss after TURP, should surgery become necessary [9]. A trial without catheter (TWOC) is considered preferable to leaving a catheter in place; success rates of 23–28% have been reported [10,11], but significant numbers of patients still require TURP, either as an emergency or electively.

The functional symptoms of BPH can be reduced by α-blockers such as tamsulosin [12], which improve flow rates and bladder emptying, and it is thought likely that they also help to reduce bladder outlet resistance by effects on the sympathetic tone of the bladder neck and prostate stroma [13]. By reducing this resistance, the patient retains sufficient detrusor function, α-blockers could help relieve AUR and improve the chances of a successful TWOC [14]. The optimum duration of treatment with α-blockers has not been fully assessed, and there is controversy about the length of time the catheter should remain in situ for the initial treatment phase. One study suggested that more prolonged use of indwelling catheters has better success rates for TWOC; immediate withdrawal had a 44% success rate compared with 62% if the catheter was left for 7 days [15].

Tamsulosin is an α1-blocker with particular affinity for the α1A receptors that predominate numerically and functionally in

OBJECTIVE

To evaluate the efficacy of tamsulosin compared to placebo for treating catheterized patients with acute urinary retention (AUR) caused by benign prostatic hyperplasia (BPH), by comparing the numbers of patients who voided successfully after removing their catheter.

PATIENTS AND METHODS

This was a randomized, double-blind, placebo-controlled, parallel-group, multicentre study. Men with AUR secondary to BPH were catheterized and then, if they fulfilled the entry criteria, were randomly assigned to receive either 0.4 mg tamsulosin hydrochloride in a modified-release capsule once daily, or a placebo. After up to eight doses the catheter was removed and the ability to void unaided assessed.

RESULTS

In all, 149 men (mean age 69.4 years) were randomly assigned to receive tamsulosin (75) or placebo (74); eight were not evaluable, so the intent-to-treat population was 141 men. Thirty-four men taking tamsulosin and 18 taking placebo did not require re-catheterization on the day of the trial without catheter (48% and 26% respectively, P = 0.011; odds ratio 2.47, 95% confidence interval, CI, 1.23–4.97). Success using free-flow variables was also higher in the men who received tamsulosin, at 37 (52%) vs 24 (34%) on placebo (P = 0.019; odds ratio 2.34, 95% CI 1.15–4.75). Withdrawals were high (120 men, 81%), mostly because of a need for re-catheterization (89 men, 60%). Dizziness and somnolence occurred in seven (10%) and four (6%) men who received tamsulosin, and two (3%) who received placebo, but overall the incidence of adverse events was similar in the two groups. One patient died from carcinomatosis.

CONCLUSION

Men catheterized for AUR can void more successfully after catheter removal if treated with tamsulosin, and are less likely to need re-catheterization. The side-effect profile was similar for tamsulosin and placebo, and consistent with known pharmacology. From these results tamsulosin can be recommended for treating men after catheterization for AUR, and can reduce the likelihood of the need for re-catheterization.

KEYWORDS

acute urinary retention, BPH, trial without catheter, tamsulosin
### PATIENTS AND METHODS

Between March 1997 and December 2000, 149 men aged 51–91 years (mean 69.4) were entered into the study, and randomly assigned to receive tamsulosin hydrochloride in a modified-release capsule once daily (75 patients) or placebo (74): the intent-to-treat (ITT) population was 141 patients. All had been admitted to hospital through the Accident and Emergency Department with evidence of renal or hepatic dysfunction; previous surgery on the urinary tract; other diseases of the bladder; any malignancy; retention-enhancing medications; allergies; and severe cardiac disease. The study received Ethics Committee approval and conformed to the international guidelines for clinical trials; it was conducted according to the Declaration of Helsinki and all patients gave fully informed written consent. A Clinical Trials Exemption was granted by the Medicines Control Agency, and a Clinical Trial Certificate by the Irish Medicines Board. Eight hospitals in the UK and one in Ireland participated.

Patients catheterized for AUR were invited to participate when comfortable. The time between catheterization and the first dose of study medication was ≤72 h. Medication was given once daily, after breakfast or lunch for the first dose, then after each day’s breakfast; the duration of treatment was decided by each site to be either three or eight doses, according to their normal practice. Patients were allowed to go home after a successful catheter-free void, defined as a flow rate of >5 mL/s, >100 mL voided volume, and a residual volume of ≤200 mL. In the absence of any internationally agreed outcome measures for the success of a TWOC, these definitions were regarded by the investigators as a reasonable reflection of successful bladder emptying. Patients could continue to take the medication for up to 26 weeks, but if re-catheterization was needed they were withdrawn from the study.

### RESULTS

The predetermined primary criteria for defining a successful TWOC showed no significant benefit of tamsulosin over placebo (34% vs 24%, \( P = 0.193 \), Table 1). The results presented are a secondary analysis of this study. Analysing any two free-flow criteria, tamsulosin gave a significantly better outcome than placebo (Table 1). Patients who received tamsulosin were less likely to need re-catheterization than those who received placebo (Fig. 1); 34 patients who received tamsulosin and 18 who received placebo did not require re-catheterization (48% vs 26% success, \( P = 0.011 \); odds ratio 2.47, 95% CI 1.23–4.97).

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### TABLE 1 Analysis using free-flow criteria, as n (%) of patients in subgroups with a successful result

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Tamsulosin</th>
<th>Placebo</th>
<th>Total</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>N patients</td>
<td>71</td>
<td>70</td>
<td>141</td>
<td></td>
</tr>
<tr>
<td><strong>Outcome by criteria</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary analysis</td>
<td>24 (34)</td>
<td>17 (24)</td>
<td>41 (29)</td>
<td>0.193</td>
</tr>
<tr>
<td>Any two free-flow criteria</td>
<td>41 (58)</td>
<td>28 (40)</td>
<td>69 (49)</td>
<td>0.02</td>
</tr>
<tr>
<td>Two specified criteria*</td>
<td>37 (52)</td>
<td>24 (34)</td>
<td>61 (43)</td>
<td>0.019</td>
</tr>
<tr>
<td>Any two criteria†</td>
<td>43 (61)</td>
<td>29 (41)</td>
<td>72 (51)</td>
<td>0.013</td>
</tr>
<tr>
<td><strong>Outcome by age, years (primary analysis)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50–59</td>
<td>3 (38)</td>
<td>5 (50)</td>
<td>8 (50)</td>
<td></td>
</tr>
<tr>
<td>60–69</td>
<td>10 (40)</td>
<td>6 (24)</td>
<td>16 (32)</td>
<td></td>
</tr>
<tr>
<td>70–79</td>
<td>10 (33)</td>
<td>5 (16)</td>
<td>15 (25)</td>
<td></td>
</tr>
<tr>
<td>&gt;80</td>
<td>1 (13)</td>
<td>1 (25)</td>
<td>2 (17)</td>
<td></td>
</tr>
</tbody>
</table>

Primary analysis: three criteria, i.e. flow rate >5 mL/s, voided volume >100 mL, residual ≤200 mL; *Flow rate >5 mL/s, voided volume >100 mL; †Flow rate >5 mL/s, voided volume >100 mL, residual ≤250 mL.
Of the patients who received tamsulosin, those taking eight doses before catheter removal were less likely to need re-catheterization than those taking three doses (53% vs 46%). A higher proportion of eight-dose patients had a successful outcome, using the original definitions, than the three-dose patients (38% vs 27%) but this difference was not significant (P > 0.1) and this issue was not factored into any of the subsequent analyses. In all, 120 patients (81%) did not complete both phases of the study; most of these (89, 69%) were because of the need for re-catheterization at the end of the acute phase of the study. Because of the high loss rate there were too few patients remaining in the study after the initial measurements for a valid analysis of long-term efficacy after AUR. There was no significant difference between age groups in the outcome of successful voiding when analysed by the free-flow criteria (Table 1), but the there were too few patients aged >80 years to allow meaningful conclusions to be drawn.

SAFETY

The adverse-event profile was as expected for this class of drug, and the incidence of adverse events similar in the two groups. Exceptions were dizziness and somnolence, which occurred in seven (10%) and four (6%) patients who received tamsulosin, and two (3%) and two (3%) receiving placebo. Both events are recognized with α-blocker use, although perhaps because there were many elderly patients in the study their incidence was higher than the known tolerability profile of tamsulosin. Fewer than half of the patients had adverse events. More patients who received tamsulosin withdrew for adverse events or adverse experiences (seven, 9%) than those who received placebo (one, 1%), but only five had an adverse event probably related to tamsulosin (three incidences of dizziness, and one each of somnolence and dry mouth). None of these adverse events were serious. One patient in the tamsulosin group died during the study, the cause of death being noted as carcinomatosis, but the site of the primary tumour was not given. This death was classified as unlikely to be related to the test drug.

DISCUSSION

The primary objective of the present study was to evaluate the efficacy of tamsulosin compared with placebo for treating catheterized patients with AUR caused by BPH, by comparing those voiding successfully after removing their catheter. The predetermined primary criteria for defining a successful TWOC showed no significant benefit of tamsulosin. However, because the initial criteria gave few successful TWOCs it was decided, before breaking the randomization code, to use secondary analyses for revised criteria of success. The definition of ‘success’ in the treatment of AUR has yet to be universally agreed. For patients it must, at least in part, relate to the lack of need for re-catheterization. Patients in the tamsulosin group had an odds ratio in their favour of 2.47 of not requiring re-catheterization before being sent home. For success as defined by the investigator, the odds ratio in favour of tamsulosin was 2.22. When assessed by any two free flow criteria (flow rate, voided volume and residual volume) patients on tamsulosin were more likely to void successfully in the acute phase.

After the present study was designed the use of re-catheterization rates as a clinical marker was reported in two studies comparing alfuzosin and placebo, both taken for 24 h after catheterization. One was a small pilot trial and the other a multicentre randomized controlled trial in which the criteria for assessing the success of TWOC were simply the voiding of urine and lack of need for re-catheterization [17–19]. A similar study with alfuzosin showed a significant difference in outcome by age; younger patients were more likely to have a successful TWOC [17], but in the present study the efficacy was similar across the age range. The patients in the present study were elderly (mean age 69.4 years), but the efficacy results were no different from those expected for younger groups.

In the present trial some patients were catheterized for only 3 days and others for 8; this allowed for variations in practice between hospitals and the distribution was equal for both study groups. Differences in outcome between 3- and 8-day patients were not statistically significant, but the study may not have had the power to detect such a difference. The distribution of patients was equal in both study groups, and so is unlikely to have affected the analysis of whether the treatment effects of tamsulosin differ from those of a placebo.

The safety profile was as expected for an α-blocker, although the incidence of some adverse events was higher than published for tamsulosin, possibly because of the greater average age of the present men. Less than half of the patients reported adverse events, and none were serious. One patient died from unrelated carcinomatosis, despite any known malignancy being a contraindication to participation.

Many questions remain unanswered about the use of α-blockers in the clinical setting. It is still not possible to predict which patients are likely to respond to α-blockers and which are not; the study was not powerful enough to answer this. There were also insufficient data to draw conclusions about long-term outcomes for patients treated with tamsulosin; it is a pity, in retrospect, that the study was not designed to follow patients who were re-catheterized as well as those who were not. Published data from untreated patients suggest that many will require re-catheterization or surgical intervention; 84% had surgery within 5 years in one study [20]. It would be valuable to study the long-term use of tamsulosin after catheterization for AUR. Work with another α-blocker, alfuzosin, shows that treatment for 6 months was associated with a significantly lower incidence of de novo AUR than with placebo (0.4% vs 2.4% [21]). A retrospective analysis of five studies of the long-term use of α-blockers for treating BPH showed that the incidence of AUR was significantly lower in patients taking this group of drugs, and there was a possible reduction in the need for surgery [22].

Currently, only one α-blocker licensed in Europe for treating BPH has the management of AUR as an indication. From the present results, tamsulosin can also be recommended for treating patients after catheterization for AUR, and can significantly reduce the likelihood of the need for re-catheterization, at least acutely.

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List of Trialists: Mr A Arnold, Queen Elizabeth Hospital, Birmingham; Mr C Bunce, Barnet General Hospital; Mr M Hehir, Stirling Royal Infirmary; Mr E Kiely, Cork University Hospital; Mr M Lucas, Morriston Hospital, Swansea; Mr P McInerney, Derriford Hospital, Plymouth; Mr V Nargund, Homerton Hospital, London.

LUCAS ET AL.
TAMSULOSIN IN THE MANAGEMENT OF ACUTE URINARY RETENTION

and St Bartholomew’s Hospital, London; Mr T P Stephenson, University Hospital of Wales, Cardiff; Mr H Whitfield, Central Middlesex Hospital, London.

CONFLICT OF INTEREST
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Abbreviations: AUR, acute urinary retention; TWOC, trial without catheter; ITT, intent to treat.
A prospective evaluation of efficacy and compliance with a multistep treatment approach for erectile dysfunction in patients after non-nerve sparing radical prostatectomy

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OBJECTIVE
To assess the response rate to different erectile aids in a consecutive series of patients treated with non-nerve sparing radical prostatectomy (NNSRP).

PATIENTS AND METHODS
Ninety-four potent men were counselled about the different treatment options to restore an assisted erection before they had NNSRP. They were invited to participate in a multiphase protocol involving the sequential use of different erectile aids which aimed at restoring erectile function after surgery. The first proposed treatment was oral apomorphine sublingual. Patients with a positive response to the 1-item overall efficacy question and a minimum score of 3 in both question 3 and 4 of the International Index of Erectile Function were considered responders to oral pharmacotherapy. Treatment with sildenafil was then suggested to those not responding. If patients did not respond to oral pharmacotherapy a trial with a vacuum erectile device was offered; those not responding to this were then offered intracavernosal injection therapy with prostaglandin-E alone as the first option, followed by a mixture of vasoactive agents if needed. In those in whom injections also failed, a penile implant was recommended. At the 1-year follow-up visit all patients were offered a second trial with oral therapy regardless of the treatment currently in use.

RESULTS
Seventy-six patients entered the protocol; there was no response to apomorphine. Five of 59 (8%) patients responded to sildenafil when they first used it at a mean of 7 months after NNSRP, while there were three additional responders in 22 patients who tried it for a second time a year later. Of patients achieving at least a complete tumescence sufficient for vaginal penetration, 52% and 60% were considered responders to the vacuum device and intracavernosal injections, respectively. Overall, 44% of patients enrolled in the protocol chose to use an erectile aid for at-home use. At the 1-year follow-up, only 20% of patients were still using an erectile aid, including two who had had a penile implant.
CONCLUSIONS

Up to 10% of patients may achieve a clinically significant erection with sildenafil after NNSRP, but 80% will not be using any erectile aid at 1 year after surgery. In the present study protocol the proposed erectile aids were largely inadequate for treating the permanent erectile dysfunction that follows NNSRP.

KEYWORDS

radical prostatectomy, erectile dysfunction, oral treatment, intracavernosal injections, vacuum pump.

INTRODUCTION

Radical prostatectomy (RP) is commonly used for organ-confined prostate cancer [1] and has been developed with the addition of techniques to preserve the neurovascular bundles, allowing the prostate to be completely excised while maintaining sexual function [2]. However, a significant proportion of men undergoing a nerve-sparing procedure fail to recover spontaneous erectile function. Also, both oncological and surgical factors mean that many RP are not nervesparing (NNSRP). Patients with bilaterally transected neurovascular bundles are not expected to regain any spontaneous erection [3], and permanent erectile dysfunction (ED) remains an important issue in patients with prostate cancer, with a significant impact on their health-related quality of life [4].

Despite the many reports on nerve-sparing series, few have assessed the use of the available erectile aids as permanent treatments after NNSRP. A recent American survey reported that many patients after NNSRP use no treatment for ED, and that the few reports of treatment failed to provide sexual quality-of-life measures comparable with men regaining spontaneous erectile function [5]. By contrast, up to 85% of patients predominantly having NNSRP were still using erectile aids effectively at 1 year after surgery in a series from Israel [6]. Our knowledge no study has prospectively evaluated different treatment alternatives for ED in a selected series of patients after NNSRP.

Studies of the efficacy of oral treatment after NNSRP are based on small series reporting a response rate to sildenafil of none [7] to 15% [8]. Intracavernosal pharmacotherapy still remains the main treatment option for patients who fail to recover spontaneous erections after RP, and high response rates have been reported using mixtures of vasoactive agents [6,9]. The present study was designed to evaluate the efficacy and the patients’ compliance with currently available treatments for ED. A consecutive series of patients who had RP with NNS intent were invited to participate in a multistep trial which offered a sequence of treatments for ED, starting from the less-invasive oral tablets and the vacuum pump, and then moving to second-line therapies, represented by intracavernosal injections (ICIs), and finally to the third-line prosthetic therapy, as outlined in the European Association of Urology guidelines [10].

PATIENTS AND METHODS

From January 2001 to October 2002, 152 patients treated at the first author’s institution had a NNSRP. Eligibility for surgery was based on a local protocol adopted at our institutions since 1998, and involving extensive indications for retropubic RP, i.e. all patients with prostate cancer confirmed by biopsy, a negative bone scan and a life-expectancy of ≥10 years were offered surgery, regardless of PSA level at presentation, Gleason score and DRE findings.

Indications for excising nerve bundles were one or more of the following: bilateral positive biopsies, Gleason score >7, a DRE suggestive of extracapsular tumour extension, age >70 years, PSA >20 ng/mL. In the absence of precise published guidelines on when the nerves should be spared, these criteria represented the personal view of the members of the institutions where the study was conducted. All patients were requested to complete the International Index of Erectile Function (IIEF) questionnaire before RP [11]; 94 reporting an erectile function (EF) domain score on the IIEF of ≥25 [12] received early counselling after RP on the different treatment options to restore an assisted erection, including penile prostheses. Based on early results from our recently published data [13], patients were advised that any nonsurgical treatment would be of maximum benefit if started within 3 months after surgery. Patients were then given the opportunity to attend a specialized andrology outpatient clinic at any time during the follow-up.

Patients presenting to the andrology clinic at any time after RP (Visit 1) were invited to take part in a multiphase protocol involving the sequential use of different erectile aids which aimed to restore erectile function, provided they had not recovered spontaneous erectile function.

Because oral apomorphine sublingual (SL) had been recently released on the Italian market, the patients’ request for this was significant and we subsequently adopted this drug as the first proposed treatment in the protocol. Four sample doses of apomorphine SL 3 mg were supplied to be taken ‘as required’, not exceeding one dose in any 8-h period. Patients were instructed to take one tablet of apomorphine SL 15 min before attempting sexual intercourse and to allow it to dissolve after placing it under the tongue. Treatment response was assessed with the one-item overall efficacy question (OEQ), ‘Has the treatment you have been taking over the past two to four weeks improved your erections?’, and with the EF domain questionnaire. Those with a positive response to the OEQ and with a minimum mean score of 3 above baseline for both questions 3 and 4 of the IIEF were considered responders.

Those not responding were then offered treatment with sildenafil and assessed using the same criteria for response as for apomorphine. A trial with a vacuum erection device was offered as the first-line option to those patients who had no response to both oral agents. Patients achieving at least a grade III erection, i.e. a complete tumescence sufficient for vaginal penetration, were considered responders. ICI using prostaglandin-E (PGE), followed by a mixture of vasoactive agents if necessary, was regarded as a second-line treatment if the vacuum device failed. If ICIs also failed to produce at least a grade III erection, a penile implant was recommended. Patients were allowed to change to a different treatment at any time.

Data on pathological stage, Gleason score and concomitant adjuvant treatment were also recorded during the first visit. The current status of continence was categorized as: no significant incontinence, mild incontinence (less than one moist pad per day) and marked incontinence (one or more wet pad per day).
Visit 2 was scheduled for 4 weeks afterward; those not responding to apomorphine as documented by the OEQ and the EF domain score were instructed to take a tablet of sildenafil 1 h before sexual intercourse, provided they had no contraindications to phosphodiesterase type 5 inhibitors [10], and were supplied with four doses of 100 mg for a 4-week home trial. Patients were considered for evaluation if they had taken at least two of the four tablets dispensed for any oral treatment.

When sildenafil also failed to produce a positive response, patients were instructed in the use of the vacuum erection device at Visit 3 (Somablue, Atlanta, USA). The erection obtained after placing the constriction band was categorized into four grades by the same doctor, according to objective examination criteria as previously described [14]. To assess the discomfort experienced during the use of the device patients were asked to score the pain on a 10-cm visual analogue scale (VAS), where ‘0’ meant no pain and ‘10’ the maximum pain [15]. All patients were supplied with a device (electric or manual, depending on their preference) and an informative videotape for a 4-week home trial if desired.

When returning the vacuum erectile device at Visit 4, information about buying a device was provided to interested patients, while those not responding were offered ICI; a 20-μg injection with PGE was administered initially and subsequent doses were individually titrated depending on the erectile response obtained after the first injection. When there was an unsatisfactory response to a full dose of PGE (20 μg), a mixture of papaverine 10–20 mg and phentolamine 1–2 mg was added to PGE. Patients with a positive response, i.e. at least a grade III artificial erection, were taught self-injection for home use, and those not responding were recommended a penile implant.

Follow-up visits or telephone calls were scheduled at 6 and 12 months to assess any discontinuation of treatment. A further trial with both apomorphine SL and sildenafil was offered 1 year after visit 1 and the results assessed with the OEQ and the EF domain score.

A paired t-test for matched variables was used to compare the IIEF and the VAS scores before and after therapy, with the chi-square test to compare proportions (i.e. responders vs. non-responders).

### RESULTS

Of the 94 men potent before RP and counselled on the early use of erectile aids, 77 (mean age 65.6 years, SD 6.7) attended the andrology clinic. The mean (SD) time between RP and self-referral to the andrology clinic was 6.5 (3.49) months. One patient who had RP 3 months earlier recovered spontaneous erections and was thus excluded from the study. The 76 remaining patients reported a mean (SD) EF domain score after RP of 4.64 (6.3) and were eligible for the protocol.

The patients’ characteristics (pathological stage, Gleason score and adjuvant treatment) are listed in Table 1.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathological stage</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>50 (66)</td>
</tr>
<tr>
<td>T3a</td>
<td>14 (18)</td>
</tr>
<tr>
<td>T3b</td>
<td>9 (12)</td>
</tr>
<tr>
<td>T4</td>
<td>3 (4)</td>
</tr>
<tr>
<td>N+</td>
<td>8 (10)</td>
</tr>
<tr>
<td>N0</td>
<td>20 (26)</td>
</tr>
<tr>
<td>Nx</td>
<td>48 (63)</td>
</tr>
<tr>
<td>Gleason score after RP</td>
<td></td>
</tr>
<tr>
<td>4–6</td>
<td>43 (57)</td>
</tr>
<tr>
<td>7</td>
<td>17 (22)</td>
</tr>
<tr>
<td>8–9</td>
<td>16 (21)</td>
</tr>
<tr>
<td>Adjuvant treatment</td>
<td></td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>10 (13)</td>
</tr>
<tr>
<td>Hormone therapy</td>
<td>11 (14)</td>
</tr>
<tr>
<td>Radiotherapy + hormone therapy</td>
<td>2 (2.5)</td>
</tr>
</tbody>
</table>

Figure 1 shows the flow chart relative to oral therapy. No patient failed to take the minimum of four tablets required for evaluation. Two of the 76 patients (2.6%) taking apomorphine SL answered ‘yes’ to the OEQ although the improvement for both Q3 and Q4 was below the level for them to be considered responders. Eight of 59 patients (13.5%) receiving sildenafil answered ‘yes’ to the OEQ but only five (8%) were considered responders. Three of them were discharged from the clinic with a prescription and the remaining two requested to proceed to the next step of the protocol. Neither of the two patients reporting marginal benefit after apomorphine responded to sildenafil. The overall mean (SD) EF domain score after apomorphine was 4.65 (1.97), and comparable with that at baseline (P = 0.978). The improvement of mean EF domain score after sildenafil for all patients, at 6.14 (5.08), was statistically (P = 0.01) but not clinically significant.

Side-effects were reported by nine of 75 patients (12%) after apomorphine SL (nausea in six, vomiting in two and headache in one) and by seven of 59 (12%) after sildenafil (headache in all).

Figure 2 shows the flow chart followed by the 74 patients who did not respond to oral therapy; 17% refused a trial with the vacuum erectile device and opted for ICI with PGE. Overall, 98.5% of patients received a full dose of PGE, including all but one of the 33 responding to the vacuum device. The PGE response rate (60%) did not significantly differ from that for the vacuum device (52.5%) (chi square, P = 0.764). The mean VAS score recorded after using the vacuum device, at 2.57 (0.78), was significantly lower than after PGE, at 2.91 (0.96) (P = 0.02). Three patients developed priapism after ICI with PGE. There was a statistically significant correlation between PGE response status and vacuum response status (chi square, P = 0.054). Data on treatment response rate and the percentage of patients who chose an erectile aid for at-home use are summarized in Table 2.

There were three deaths during the 1-year follow-up (two cancer-related, one other causes). All the remaining patients (73) were reviewed either at the clinic or by telephone. Two patients received a penile implant during the first year of follow-up in our institution (one had discontinued PGE, the other was not satisfied with the vacuum device). No patient recovered spontaneous erectile function. The numbers of patients who discontinued treatment after 1 year are shown in Table 2; overall, 17 (23%) were still using some erectile aid at 1 year. Apomorphine was not offered at the 1-year follow-up because of its poor efficacy. Twenty-two patients initially not responding to oral treatment attempted a second trial with sildenafil; three (14%) then responded, according to the previous criteria, and two decided to use the treatment at home.

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**TREATMENTS FOR ED AFTER NON-NERVE SPARING RADICAL PROSTATECTOMY**

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**TABLE 1 The patients’ characteristics, including pathological stage, Gleason score and adjuvant treatment, for the 76 men potent before NNSRP and referred to the andrology clinic**

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DISCUSSION

Sexual bother is becoming a key issue for patients with prostate cancer who choose radical surgery. In a recent study [4] sexual dysfunction was an independent determinant of worse general health-related quality of life after primary treatment for prostate cancer. A retrospective analysis showed that men undergoing NNSRP reported worse quality-of-life scores for sexual function than patients treated with NSRP [5]. Previous questionnaire-based surveys indicated that most patients with ED after RP used no erectile aids, but the reason for this could not be identified [5,16]. The present study focused on a selected series of patients with normal sexual function before RP who then had NNSRP and received standard counselling on the current view of how to optimize sexual response using erectile aids [13,17]. Of the counselled patients, 82% attended the ED clinic and entered the multiphase treatment protocol, a finding which suggests that a large proportion of men potent before RP are interested in regaining normal sexual function afterward.

None of the two types of oral compounds currently used to improve sexual function is expected to be effective if the cavernosal nerves are transected at the time of surgery. Apomorphine SL cannot enhance the neurological signalling to sexual stimuli delivered from the CNS to the periphery if the cavernosal nerves are interrupted [18]. Similarly, no amplification of the nitric oxide cascade should occur after giving a phosphodiesterase-5 inhibitor in the absence of nitric oxide release from intact cavernosal nerve fibres. Despite these physiopathological considerations, the present study design was supported by the lack of sufficient clinical evidence to discourage oral treatment as a first-line option in this patient category, as

FIG. 1. Flow chart of 95 men potent before RP who were counselled on early erectile treatment after NNSRP and tried oral treatment.

Patients counselled: 95
Attended the clinic: 78

Excluded because of spontaneous erections: 1

Refused Apomorphine: 1
Received Apomorphine: 76

Nonresponders: 76
Responders: 0

Refused Sildenafil: 9
Sildenafil contraindicated: 8
Received Sildenafil: 60

Nonresponders: 55
Responders: 5

Patients asking for other treatment options: 2
Discharged with Sildenafil: 3

Offered a trial with vacuum erectile device: 74
outlined by the European Guidelines [10]. Also, there is increasing evidence that a few patients may either recover spontaneous erectile function or respond to oral treatment after NNSRP, implying the existence of unrecognized residual nerve tissue or a non-neurogenic mechanism. Zagaja et al. [7] reported that sildenafil was ineffective in all 33 patients who had bilateral transection of neurovascular bundles during RP. Conversely, Zippe et al. [8] found four responders among 26 NNSRP patients treated with sildenafil. In the present study all patients accepted the initial treatment with apomorphine SL, an oral agent that significantly improved erectile function in a series of patients with ED of various causes [19]. Apomorphine SL became available when the present study started and many patients were motivated to try it because of its rapid onset of action, lack of cardiovascular contraindications, and safety profile. To our knowledge there is no previous report on its use after NNSRP; however, it was ineffective in this series.

Fifty-nine patients who did not respond positively to apomorphine reported an 8%
response rate to sildenafil. This not responding were offered an additional trial during the 1-year follow-up visit, in line with previous observations that sildenafil may not be effective in the first 6 months after surgery [7], and that the regeneration of partially damaged nerves may take up to 2 years [20]. An additional 13% response rate was documented in this small series. The present data suggest that, after NNSRP, treatment with a phosphodiesterase-5 inhibitor may be worthwhile, particularly at 1 year after RP.

The European guidelines suggest that the use of a vacuum erectile device should be regarded as a first-line option when oral treatment fails, and to consider ICI as a second-line treatment [10]. High response rates and long-term efficacy were reported for both of these erectile aids [17]. There was a 60% response rate for PGE, the only drug licensed for ICI, in the present series; 85% success rates were reported in other studies when using a mixture of vasoactive agents [6,21].

A randomized study excluding patients after RP showed a trend favouring ICI because there were fewer side-effects and greater patient satisfaction [22]. Conversely, in the present analysis of this unrandomized series, ICI was judged more painful than the vacuum device. The proportion of patients choosing ICI for domestic use was as low as 16% and comparable with the vacuum device. By contrast, Daniel et al. [6] found that all of the 85% of patients in that series who responded to a mixture of vasoactive drugs used the treatment at home. In the present study almost half the patients discontinued after 1 year for both the vacuum device and ICI. Although these values may depend on several variables not addressed by the current study, there are similarities with previous American series [17,23]. Overall, only 44% of patients enrolled in the protocol chose to use an erectile aid at home. Again, these data are comparable with previous retrospective studies on unselected patients [16].

European Guidelines state that for patients who fail pharmacological therapy or who prefer a permanent solution to their problem, surgical implantation of a prosthesis may be considered [10]. All the present patients received counselling before RP on the excellent satisfaction rate after a penile implant for ED [24]. Those not responding to all the proposed treatments were offered the option of having an inflatable prosthesis implanted at no cost, under the Italian national health system. However, only two patients had a prosthesis implanted within a year from NNSRP. This seems to suggest that the currently available erectile aids are largely inadequate for treating the permanent ED that results from NNSRP.

However, the possibility of a design bias should be considered when interpreting the present results. The overall poor response rate to oral treatments raises doubts about the appropriateness of the sequence of treatments adopted. The use of a drug such as apomorphine, which was then ineffective in most patients with ED, as a first choice in a rehabilitation protocol may have produced a detrimental effect on the overall compliance with treatment. The subsequent administration of another oral compound, sildenafil, with a 90% failure rate, could have compromised patients’ expectations of any subsequent therapy proposed. The primary objective of the study was to assess the efficacy of different erectile aids administered in a sequence that reflected the recommendations in the European guidelines. From the results it appears that oral compounds may not be an appropriate first choice after NNSRP. In our current practice these patients are now offered ICI or the vacuum device as the first option, with a change to oral sildenafil suggested no earlier than 1 year from surgery.

In conclusion, this study provided information that may be useful in the sexual counselling of patients before and after NNSRP. The recovery of spontaneous erectile function is rare after NNSRP; up to 10% of patients may benefit from the use of sildenafil, while apomorphine SL had no role in treating this type of erectile failure. The overall response rate to the available nonsurgical treatments may be influenced by individual motivation but it should not be expected to be more than 50–60%. This study indicates that half of patients are likely to discontinue treatment within a year. Treatment of ED after NNSRP remains a difficult and frustrating task for the urologist. Patients assessed in the present series appeared to be motivated to regain erectile function, as they were sexually active before surgery and chose to seek treatment. Surprisingly, only 20% of the patients were still using an erectile aid after 1 year, a situation that warrants future efforts to seek more effective treatments. Different protocols not using oral compounds as the initial treatment may prove less frustrating for patients and thus produce less disappointing results.

**CONFLICT OF INTEREST**

None declared.

**REFERENCES**


3. Sachs BD, Liu YC. Maintenance of erection of penile glans, but not penile

---

**TABLE 2**

<table>
<thead>
<tr>
<th>Option</th>
<th>Responders</th>
<th>Choosing at-home use</th>
<th>Discontinuing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apomorphine</td>
<td>0/76</td>
<td>60</td>
<td>0</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>initial</td>
<td>5/59 (8)</td>
<td>2/3</td>
</tr>
<tr>
<td></td>
<td>1-year*</td>
<td>3/22 (14)</td>
<td>0/3</td>
</tr>
<tr>
<td>Vacuum</td>
<td>32/61 (53)</td>
<td>13/32 (40)</td>
<td>6/13</td>
</tr>
<tr>
<td>ICI PGE</td>
<td>44/73 (60)</td>
<td>15/44 (34)</td>
<td>10/15</td>
</tr>
<tr>
<td>ICI cocktail†</td>
<td>4/5</td>
<td>2/4</td>
<td>2/2</td>
</tr>
</tbody>
</table>

*Patients originally not responding to oral treatment; †Patients not responding to PGE alone.
TREATMENTS FOR ED AFTER NON-NERVE SPARING RADICAL PROSTATECTOMY

9 Dennis RL, McDougal WS. Pharmacological treatment of erectile dysfunction after radical prostatectomy. J Urol 1988; 139: 775–9
21 Dennis RL, McDougal WS. Pharmacological treatment of erectile dysfunction after radical prostatectomy. J Urol 1987; 139: 775–6

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email: gontero@med.unipmn.it

Abbreviations: (N)(NS)RP, (non)-nerve-sparing radical prostatectomy; ED, erectile dysfunction; IC, intracavernosal injection; II(EF), International Index of Erectile Function; SL, sublingual; OEQ, overall efficacy question; PGE, prostaglandin-E; VAS, visual analogue scale.
Risk factors in predicting a poor response to sildenafil citrate in elderly men with erectile dysfunction

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Department of Urology, Seoul National University Hospital, Seoul, Korea
Accepted for publication 24 August 2004

OBJECTIVE
To assess the clinical efficacy of sildenafil and the potential predictors of poor response to sildenafil in elderly patients with erectile dysfunction (ED).

PATIENTS AND METHODS
The study included 162 patients (aged ≥60 years) treated with sildenafil for at least 8 weeks; all patients were evaluated with a history, physical examination, measurement of total testosterone and a pharmacological erection test. Sexual function before and 8 weeks after treatment was assessed using the self-administered International Index of Erectile Function (IIEF). Treatment was considered successful when the patient attained a higher grade on the erectile function (EF) domain score, and an affirmative response to the overall assessment question. Factors influencing treatment outcome were evaluated by univariate and multivariate statistical analysis.

RESULTS
The overall efficacy with sildenafil was 47% (76/162). On univariate analysis, uncontrolled diabetes, current smoking, hypogonadism (<3 μg/L testosterone) and low pretreatment EF domain score (<17) were selected as predictors of a poor response. On multivariate logistic regression, a low pretreatment EF domain score was the strongest independent prognostic factor for a poor response (odds ratio 2.25, 95% confidence interval, 1.45–7.33), and this was followed by hypogonadism (1.89, 1.12–3.16) and current smoking (1.34, 1.04–3.52).

CONCLUSION
In a real clinical setting, sildenafil was effective for about half of the elderly men. The baseline EF domain score, hypogonadism and current smoking were significantly associated with failure of sildenafil. These results suggest that modifying reversible risk factors, e.g. stopping smoking and replacing testosterone, would be beneficial in augmenting the efficacy of sildenafil in elderly men.

KEYWORDS
testosterone, smoking, erectile dysfunction

INTRODUCTION
While erectile dysfunction (ED) is not a life-threatening condition it may result in withdrawal from sexual intimacy and reduce the patient's quality of life. Several epidemiological studies [1,2] show that the prevalence of ED is strongly associated with ageing and the presence of concomitant chronic disease (diabetes, hypertension, depression) or smoking habits.

The introduction of sildenafil into the management of ED has led to major changes in disease management. The improvement rate for erection in clinical studies is ~74% and 82% with doses of 50 mg and 100 mg, respectively [3]. However, for some groups of patients sildenafil often does not work effectively, as shown in clinical studies [3–5]. For patients with a history of radical prostatectomy or current diabetes, the efficacy is significantly less, by 20–30%. In addition, it was reported that hypogonadism was often associated with the failure of sildenafil and correcting hypogonadism improved the response [6].

As ageing alone is an independent risk factor for ED, and as older men usually have many risk factors for ED, elderly men are likely to respond less to sildenafil than their younger counterparts. However, most clinical trials have shown no significant differences in specific age groups, although the response rate of elderly men is always lower [4], possibly because most clinical trials exclude patients with complex conditions whose inclusion might complicate the analysis of efficacy. Thus, we hypothesized that the real efficacy of sildenafil in elderly men would be less if patients with more complex comorbidities were included, as in the real clinical setting.

Thus evaluated the efficacy of sildenafil in elderly men in such a clinical setting and tried to identify risk factors associated with treatment failure. To our knowledge, there has been no study evaluating the practical efficacy of sildenafil in a trial restricted to elderly men.

PATIENTS AND METHODS
Between October 2002 and April 2003 the response to sildenafil was assessed in 162 consecutive elderly (>60 years old) patients with chronic ED. Patients were diagnosed with ED based on a self-assessment and they were eligible for inclusion in the study if they had had ED for 26 months, at least half the attempts at intravaginal intercourse had failed, i.e. double the failure rate for attempts in men with no ED [7], and they were in a stable relationship with a heterosexual partner. Patients with a history of unstable cardiac disease or those receiving any form of organic nitrate medications were excluded. All patients enrolled were naïve to sildenafil therapy.

The patients were evaluated with a complete history, a physical examination (including height and body weight), blood pressure...
RISK FACTORS FOR POOR RESPONSE TO SILDENAFIL

TABLE 1 The pretreatment factors evaluated, their distribution, and the results of the univariate analysis of the association between qualitative and quantitative factors and the response to sildenafil

<table>
<thead>
<tr>
<th>Factors</th>
<th>N (%) patients</th>
<th>Effective, n</th>
<th>Ineffective, n</th>
<th>P (chi-square)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current smoking</td>
<td>69 (43)</td>
<td>23</td>
<td>46</td>
<td>&lt;0.05</td>
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<tr>
<td>no</td>
<td></td>
<td>53</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Alcohol intake</td>
<td>51 (32)</td>
<td>27</td>
<td>24</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>no</td>
<td></td>
<td>49</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>55 (34)</td>
<td>25</td>
<td>30</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>no</td>
<td></td>
<td>51</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>Positive response to PGE</td>
<td>72 (44)</td>
<td>39</td>
<td>33</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>no</td>
<td></td>
<td>37</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>Hypogonadism</td>
<td>42 (26)</td>
<td>9</td>
<td>31</td>
<td>&lt;0.05</td>
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<tr>
<td>no</td>
<td></td>
<td>67</td>
<td>55</td>
<td></td>
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<tr>
<td>Uncontrolled hypertension</td>
<td>84 (52)</td>
<td>35</td>
<td>49</td>
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<tr>
<td>no</td>
<td></td>
<td>41</td>
<td>37</td>
<td></td>
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<tr>
<td>Uncontrolled diabetes mellitus</td>
<td>48 (30)</td>
<td>21</td>
<td>38</td>
<td>&lt;0.05</td>
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<tr>
<td>no</td>
<td></td>
<td>55</td>
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<td></td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>59 (36)</td>
<td>18</td>
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<td>no</td>
<td></td>
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<tr>
<td>Age, years</td>
<td>62.9 (3.8)</td>
<td>65.2 (2.6)</td>
<td>0.192</td>
<td></td>
</tr>
<tr>
<td>Duration of ED, months</td>
<td>43.1 (12.5)</td>
<td>47.9 (16.2)</td>
<td>0.216</td>
<td></td>
</tr>
<tr>
<td>Baseline EF domain score</td>
<td>17.6 (2.8)</td>
<td>9.6 (3.2)</td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>

All patients were initially prescribed at least four 50 mg tablets of sildenafil and were instructed to take a tablet 1 h before initiating sexual activity. The dose could be increased to 100 mg or decreased to 25 mg, based on tolerability and efficacy.

Two months later, those patients taking at least eight tablets of 50 or 100 mg of sildenafil were asked to complete the IIEF again. The overall assessment question (OAQ), ‘Has the treatment you have been taking during the study improved your ability to engage in sexual activity?’ was added at the end of the questionnaire. The treatment was considered effective when the patient moved to a higher grade of the EF domain and answered ‘yes’ to the OAQ. Any side-effects were also recorded.

STATISTICAL ANALYSIS

The treatment efficacy (effective or ineffective) was considered as a dependent variable, while the independent variables were those related to various pretreatment factors (EF domain score, current smoking, excessive alcohol intake, obesity, hypogonadism, uncontrolled hypertension, hyperlipidaemia, uncontrolled diabetes, coronary heart disease, CNS and peripheral nervous system, PNS, disease; Table 1). All qualitative variables were categorized into two groups: ‘current smoking’ included those active smokers who had a history of smoking for ≥1 year and had last smoked within 7 days [10]; ‘excessive alcohol intake’ included men who usually drank at least two drinks per day (a drink being defined as 360 mL of beer, 150 mL of wine or 40 mL of spirits at 40% alcohol) [6]; ‘obesity’ included patients whose body mass index was >30 kg/m²; ‘hypogonadism’ included patients whose total testosterone was <3 µg/L; ‘uncontrolled hypertension’ included men who had a systolic blood pressure of >140 mmHg and/or a diastolic blood pressure of >90 mmHg, with or without antihypertensive medication; ‘hyperlipidaemia’ included men who had an abnormal high value for serum cholesterol (>2.4 mg/L) or low-density lipoprotein (>1.3 mg/L); ‘coronary heart disease’ included men with a history of angina or a previous (>6 months earlier) episode of myocardial infarction; ‘uncontrolled diabetes’ included diabetic patients with evidence of poor glycaemic control (acetylated haemoglobin >7%); ‘CNS disease’ included men with, e.g. multiple sclerosis, Parkinsonism, etc.; ‘PNS disease’ included patients with PNS conditions after, e.g. radical pelvic surgery or radical prostatectomy. Because of the lower prevalence of prostate cancer in Korea, only four such patients were included. The response to intracavernosal PGE injection was also divided into two groups, i.e. E0–E3 as a negative response and E4–5 as a positive response.

A univariate analysis was used initially, applying Student’s t-test for continuous quantitative variables and the chi-square test for categorical qualitative variables. Then multiple logistic regression analysis was used to define the poor prognostic factors, the dependent variable being a poor response to treatment. The level of significance for both analyses was 5%.

RESULTS

The mean (50, range) age of the patients was 64.1 (62, 60–76) years and the mean duration of ED 45.6 (8–240) months. The baseline statistics for the various pretreatment factors
are shown in Table 1. The mean (SD) pretreatment IIEF and EF domain scores were 37.8 (8.1) and 13.1 (2.8), respectively. When the EF domain score was used to stratify the patients, 61 (38%) had severe ED, 44 (27%) moderate, 28 (17%) mild to moderate and 29 (18%) mild. There was a positive response to intracavernosal PGE injection in 85 patients (53%).

Overall, sildenafil was effective in 76 of 162 men (47%); of those responding to sildenafil, the 100 mg dose was effective in 44 (58%) and the 50 mg dose in 31 (41%), with only one man finding 25 mg effective at the end of the study.

Although there was an improvement in EF in all grades of ED, the efficacy varied according to the baseline EF; as shown in Fig. 1, the efficacy in patients with severe and moderate ED was much lower than for the other categories. The efficacy in patients with severe and moderate ED was only 31%, significantly lower than for milder grades (77%).

On univariate analysis patients with uncontrolled diabetes mellitus, current smoking, hypogonadism and a low baseline EF domain score (<17) had a poorer response to sildenafil (Table 1). Multiple logistic regression analysis was the used to assess these variables significant in the univariate analysis. Current smoking, hypogonadism and low baseline EF domain score were significantly associated with a poor response, after adjusting for the other variables (Table 2). Treatment-related adverse events were generally mild to moderate; headache (22%) and flushing (15%) were those most commonly reported.

**DISCUSSION**

Since its approval in 1998, sildenafil citrate has been shown to be effective in >100 clinical trials involving >8000 men with ED [11], but the clinical trials are designed to assess efficacy and do not necessarily reflect the real situation, i.e. specific groups of patients may be excluded from these trials because they have complicated ED. For example, patients with an uncontrolled medical illness, those receiving specific medication and those having low serum testosterone are commonly encountered in the clinical setting but are often excluded from these trials. Therefore, a few researchers [12–14] have tried to detect differences between clinical trials and the real clinical setting; the efficacy reported in these studies was 56.8–67.6%, and lower than those in clinical trials.

In the present study the focus was on elderly men (>60 years old); as elderly men commonly present in ED clinics an accurate assessments of the efficacy and of poor prognostic factors in this population is important to effectively guide these patients. As ageing is an independent risk factor for ED, and the severity of ED increases with age, elderly men are less likely to respond to sildenafil as well as their younger counterparts. However, the subgroup analysis in previous trials showed that the efficacy was not significantly influenced by ageing alone [4,15]. Therefore, in the present study we assessed the efficacy of sildenafil and identified prognostic factors for a poor response to sildenafil in elderly men. As expected, these men had a markedly poorer response to sildenafil (47%), possibly because of the population characteristics or the stringent efficacy criteria.

While sildenafil was effective in patients with mild ED it was not in those with more severe ED. According to a meta-analysis [16], the reported efficacy in patients with severe ED is 47%, clearly higher than that in the present patients in a similar category. As the present study included only elderly men this difference implies an effect of age. In addition, the present study included patients who are usually excluded from clinical trials because of other medical conditions, e.g. 42 (26%) had hypogonadism; most of them (31 of 42) did not respond to sildenafil, and this contributed to the reduction in overall efficacy.

The stringent efficacy criteria adopted here was another cause of reduced efficacy. To date the efficacy criteria of sildenafil have varied among studies, with different studies using different criteria, e.g. an improvement in IIEF score (including the EF domain or IIEF-5), at least one successful intercourse during the last 4–8 weeks, and overall assessment of erectile quality, etc. [3,4,17,18]. Because assessing erectile quality is highly subjective the efficacy of a drug for ED should be evaluated from the patients’ perspective, and thus we used the OAQ as a criterion. However, only using the OAQ risks detecting a positive response with no improvement in erectile quality (i.e. the expectation bias), e.g. = 10% of the present patients (17) positively responded to the OAQ with no improvement in their IIEF score. To reduce this subjectivity we also used the EF domain scores. Furthermore, by selecting an upgraded response rather than only an improved scores, we tried to reinforce the objectivity of the efficacy criteria.

Like the results of most efficacy studies, a low baseline EF (a lower EF domain score) was strongly associated with a poor response to sildenafil. Therefore the EF domain score should be included as a useful adjunct for diagnosis and a guide to predicting the response to the drug.

The present results also show that hypogonadism is associated with a poor
response to sildenafil. Although there remains scant evidence for a direct effect of androgen on the neurovascular mechanisms subserving ED, recent animal and human studies offer some evidence of its role in ED. In the rat penis, testosterone and its metabolite 5α dihydrotestosterone stimulated neuronal nitric oxide synthase gene expression and increased the amount of nitric oxide during erection [19]. Moreover, for aged rats, testosterone supplementation potentially restores low phosphodiesterase-5 gene expression and penile nitric oxide synthase activity [20]. In humans, patients with organic ED had a 40% lower serum free testosterone level than did those with psychogenic ED, and free testosterone levels were positively related with the peak systolic velocity and resistive index of the cavernosal arteries [21]. In addition, for patients with arteriogenic ED and low to normal androgen levels, short-term testosterone administration was reported to improve cavernosal blood flow and the response to sildenafil [22]. Considering these results it can be assumed that changes in the androgenic milieu lead to a deterioration of the haemodynamics of erection, and androgen replacement can enhance the response to sildenafil by improving cavernosal blood flow. Therefore any hypogonadal state should be corrected before sildenafil treatment. Consistent with the present results, a few recent studies showed that testosterone replacement was beneficial in some cases of sildenafil failure [6,23].

The positive response to intracavernosal PGE injection was not significantly correlated with the efficacy of sildenafil. Although PGE testing represents a cheap and easy diagnostic procedure in the office setting, this test has a high percentage of false diagnoses and its accuracy for subsequent treatment decisions is limited. In addition, the penile erection induced by PGE is mediated by cAMP, whereas that induced by sildenafil is mediated by cGMP. Therefore the sildenafil response may not be adequately assessed by testing with PGE, and we think that PGE testing should be reserved for patients failing oral pharmacotherapy, or if there is any suspicion of important vascular disease needing therapeutic intervention.

Smoking appears to be a risk factor for the endothelial dysfunction that is important pathophysiologically in ED. Acute smoking could induce blood-pressure increases and glucose intolerance by impairing microvascular function [24], and sildenafil would not improve nitric oxide-mediated endothelium-dependent vascular responses in smokers [25]. For the penis, according to the results of Guay et al. [8], reducing smoking could improve the overall efficacy of sildenafil. The present results showed that current smoking was significantly associated with a poor response to sildenafil and thus stopping smoking or even reducing consumption could be considered for enhancing the effects of sildenafil. A well-defined study might determine the time course from stopping smoking to an improved response to sildenafil.

Diabetes, often regarded as an independent prognostic factor for a poor sildenafil response in most studies, was not a statistically significant factor in the present multiple regression. The likelihood of developing ED is strongly related to the overall severity of diabetes, duration of diabetes, insulin treatment, poor metabolic control and the presence of vascular complications [26]. As we only assessed metabolic control for the present classification, this may not accurately reflect the effect of diabetes on responsiveness to sildenafil. Further refining the subclasses in this group could possibly identify those particular diabetic patients who are unresponsive to sildenafil.

There are several potential methodological limitations of the present study. Using cross-sectional methods did not allow definitive conclusions about the causal link between ED and the other investigated variables. Also, some factors that could have been important in the causes of ED could have been underestimated, e.g. only four patients with a history of radical prostatectomy were included, because there is a low prevalence of prostate cancer in Korea. In conclusion, about half of elderly men respond poorly to sildenafil; the baseline EF domain score, hypogonadism and current smoking status were significantly associated with this failure. Apart from the baseline EF domain score, the other two risk factors are reversible conditions and thus proper counselling to stop smoking, and supplementation with testosterone, are important to maximize the response to sildenafil.

CONFLICT OF INTEREST
None declared.

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Abbreviations: ED, erectile dysfunction; II(EF), International Index of (Erectile Function); PGE, prostaglandin-E; PNS, peripheral nervous system; OAQ, overall assessment question.
URETERO-URETEROCUTANEOSTOMY

LODDE et al.

OBJECTIVES

To evaluate the outcome of uretero-ureterocutaneostomy (UUC) wrapped by omentum for palliative cystectomy in symptomatic elderly high-risk patients with high-stage bladder cancer.

PATIENTS AND METHODS

The study included 15 patients (14 men and one woman, aged 72–87 years, American Society of Anesthesiology score 3) with symptomatic recurrent bleeding bladder cancer (T2/T3) who were treated with palliative cystectomy. UUC was performed by mobilizing the right pre-vesical divided ureter up to the pelvi-ureteric junction and a high retroperitoneal crossover to the divided left ureter. A stoma was created with a circular 2-cm skin excision and resecting the fatty subcutaneous tissue. Wrapped by the omentum, both well-vascularized ureteric stumps were pulled through a cross-like fascia incision up to skin level. Spatulated and everted, the ‘butterfly’ flaps were fixed to the skin and underlying omentum. Soft splints were inserted for 21 days and a Karaya ring placed.

RESULTS

The postoperative course and stoma healing was normal in 14 of the 15 patients; the sigmoid was resected because of sigmoid diverticulitis in one. The median (range) follow-up was 15 (6–24) months. There was pyelonephritis in one patient, and the dilatation of the upper tract (grade 3) in two returned to grade 2, with new asymptomatic grade 1 dilatation in one other. All patients were without stents and stoma care was provided at home.

CONCLUSIONS

This modified UUC by omental wrapping in 15 high-risk patients after palliative cystectomy was simple and safe, and their recovery was uneventful. To date the few patients with stomal obstruction were managed by J catheters, changed every 4–6 months.

KEYWORDS

uretero-ureterocutaneostomy, omental wrapping, palliative cystectomy, TCC

INTRODUCTION

Uretero-ureterocutaneostomy (UUC) was substituted by the ileal conduit almost worldwide in 1952, because stoma obstruction was common. Ureteric intubation by rubber catheters, fixed to the skin with sutures, and that became encrusted in a short period, were common and stoma care with no Karaya rings or stomal adhesive was a serious and permanent problem. Inflammation of the sutures was accompanied by the smell of infected urine, and this significantly decreased the quality of life of these patients. Despite the later arrival of polyurethane J...
The bad reputation of UUC persisted and currently is used mainly in children for decompressing dilated systems before later reconstruction. Stoma obstruction is extremely rare in the dilated thick-walled ureters of small children, where there is less subcutaneous fatty tissue.

In elderly high-risk patients with symptomatic recurrent bladder cancer, palliative cystectomy is well tolerated; complications after this surgery are mainly (30–70%) related to the urinary diversion [1–3]. Malavaud et al. [4] reported diversion-related fistulae in 16% of patients with an American Society of Anesthesiologists (ASA) score of 3; these patients are those most significantly affected by a long hospital stay, morbidity and mortality [4–6]. Therefore, the simplest form of incontinent urinary diversion, UUC, could reduce the well-known risks of ileus and pulmonary complications, and may be also welcome in laparoscopic cystectomy, currently used more often.

**PATIENTS AND METHODS**

The study included 15 patients (14 men and one woman, aged 72–87 years, ASA 3) with symptomatic recurrent and bleeding bladder cancer (T2/T3) who had a palliative cystectomy. The right ureter was divided near the bladder and mobilized carefully up to the pelvi-ureteric junction by preserving the branches of the gonadal arteries crossing the vena cava and joining the mid portion of the ureter. A high retroperitoneal crossover of the well-vascularized ureter stump, found by capillary bleeding, was done on the left side. The left ureter was divided in the same way and a stoma constructed by a 2-cm circular skin excision and excising the underlying fatty tissue down to the fascia. Incised cross-like, the rectus was divided bluntly and the posterior rectus sheath and the peritoneum also incised cross-like. The greater omentum was mostly sufficiently long, but if not was divided carefully and transferred retroperitoneally through a mesenteric window. Wrapped around the ureters (Fig. 1), the pull-through manoeuvre was used through the wide-open channel up to the surface of the skin. A sufficient blood supply of the now spatulated ureters and the omentum vessels was checked, and both ureters connected with one 5/0 poliglecaprone suture at the 3 and 9 o'clock positions (Fig. 2). The ‘butterfly’ ureteric flaps were fixed at the corners to the underlying omentum and the skin with four 5/0 poliglecaprone sutures; soft ureteric splints of 6 or 8 F were inserted (Fig. 3). A Karaya ring was placed and the wound closed.

**RESULTS**

The course after surgery was uneventful in 14 patients, with food intake and ambulation on the first day. A sigmoid resection because of diverticulitis was required 35 days after surgery in one patient. There was also pyelonephritis in this patient and this was treated, with no further complications. Stomal healing was normal and the stents were removed after 21 days in the remaining patients. Ultrasonography immediately after surgery and IVU 3 months later showed that upper urinary tract dilatation (grade 3) in two patients had returned to grade 2, and there was new asymptomatic dilatation (grade 1) in one patient. Stoma care was provided at home, with ultrasonography every 3 and later every 6 months. The median (range) follow-up was 15 (6–24) months; no splint had to be reinserted (Fig. 4).

**DISCUSSION**

UUC is the simplest form of incontinent urinary diversion, but was almost abandoned worldwide when the ileal conduit was developed in the middle of the last century. At that time the quality of life of patients with UUC was significantly reduced because stomal obstruction was common. Only rubber ureter catheters fixed to the skin with silk sutures were available, but encrusted frequently. Despite being substituted later by polyurethane J catheters, and modern stoma care with Karaya rings and adhesion, the poor reputation of UUC remained. Only in children with dilated systems is a pyelocutaneostomy or UUC still used for temporary urinary
diversion, and stomal obstruction is extremely rare. The main reasons for the latter is the better blood supply of dilated thick-walled ureters and the shorter distance between the peritoneum and the skin, with less subcutaneous fatty tissue, in children.

In contrast to Western countries, UUC is used more often in Japan; in 2001 Koshimura et al. [7] published a large series of 109 UUC, with a long-term follow-up of 17 years. The spatulated ureters were fixed to the skin with no Z-plasty, which is commonly used in Europe, and 89% of all operated patients were free of splints. However, the body mass index and the amount of subcutaneous tissue was different from that in a European or American population.

To increase the external blood supply, Roth [8] wrapped the mobilized ureters by omental flaps adapted to a midline umbilical stoma. Winter [9,10] confirmed the good results in animal experiments and in few (11) patients.

In the present series we modified the technique by mobilizing the right ureter, with a better blood supply, up to the pelvi-ureteric junction for a smooth retroperitoneal crossover manoeuvre to the left side. The blood supply of the ureteric stumps was checked by using a magnification system. Capillary arterial bleeding and spontaneous urine ejaculation are important before the connected ureters are fixed tension-free to the omentum and the skin. The same is the case for the omentum, which fills the gap between the anterior rectus fascia and the skin. Only five 5/0 poliglecaprone sutures are used to fix the corners of the ureter flaps. Stomal healing can be monitored through the Karaya ring.

For elderly patients with high-stage bladder cancer and with severe local symptoms and recurrent bleeding, palliative cystectomy is still the method of choice. In contrast to the well-tolerated bladder resection, complications are mainly related to the urinary diversion and the intestinal anastomosis [1–5]. In high-risk patients (ASA 3) even a temporary sub-ileus with an elevated intra-abdominal pressure may be followed by pulmonary insufficiency, requiring re-intubation in an intensive care unit. The same is true if there is an anastomotic leakage and a re-laparotomy becomes necessary. In one series [4], diversion-related fistulae were the most frequent major complication with the most significant effect on hospital stay. The course after surgery in the present high-risk patients was uneventful, and food intake and ambulation were possible on the next day.

There were few patients in the present study, and more complications are reported in larger series; patient selection is important. In patients treated by external beam irradiation the well-vascularized right ureteric stump may be too short for a crossover manoeuvre, and a transverse conduit must be used. However, if the stoma is obstructed, J catheters can be inserted, to be changed every 4–6 months. Also the stoma can be reconstructed by using free buccal mucosal grafts, as in a continent vesicostomy.

In summary, the modified UUC is an alternative to the standard ileal conduit in high-risk and unirradiated elderly patients with bladder cancer. Even the laparoscopic urologist might consider this simple and safe method. If the stoma becomes obstructed it can be treated with a J catheter.

**CONFLICT OF INTEREST**

None declared.

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Abbreviations: UUC, uretero-ureterocutaneostomy; ASA, American Society of Anesthesiologists.
Tubularized–incised plate urethroplasty in adults

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OBJECTIVE
To evaluate the results of tubularized incised-plate (TIP) urethroplasty for distal and midshaft hypospadias in adults, and to underline technical aspects to decrease complications.

PATIENT AND METHODS
From December 1999 to January 2004, 13 patients with hypospadias and aged 18–26 years had a TIP urethroplasty as a primary repair. Five had distal penile and eight had midshaft hypospadias. In all cases a TIP urethroplasty was used as described for children. Urinary drainage was by a urethral Nelaton catheter connected to a urine bag.

RESULTS
The catheter was removed after 10 days and the patients asked to attend a follow-up at 1, 3 and 6 months and then 6-monthly; the maximum follow-up was 3 years and the minimum was 3 months. One patient developed a fistula after the repair of distal penile hypospadias, which closed spontaneously after a month. All patients with a successful repair voided with a single straight urinary stream in a forward direction. They had a normally situated slit-like glanular meatus.

CONCLUSION
TIP repair in adults is associated good results. There is no difference in terms of wound healing, infection, complication rates and overall success between the TIP repair in children and adults. The cosmetic and functional outcome was comparable to that in children.

KEYWORDS
hypospadias, urethral plate, meatus, stenosis, tubularized incised-plate, urethroplasty, urethrococutaneous fistula

INTRODUCTION
Hypospadias is a common congenital condition, with an incidence of 3.2 per 1000 live births [1]. Various surgical procedures have been described to correct this condition. The goal of hypospadias surgery is a penis that is both functionally and aesthetically normal. This requires a penis that is straight on erection, with a vertically orientated meatus at the tip of the glans, thus promoting a single, coherent urinary stream [2]. Since its introduction in 1994 by Snodgrass [3], the tubularized incised-plate (TIP) urethroplasty, a modification of the Thiersch-Duplay technique [4,5], has become a very popular technique [4,5], has become a very popular technique for distal and midshaft hypospadias; it is associated with very good functional and cosmetic results.
Most of the studies of TIP repair are in children as such children with hypospadias in developed countries are usually treated before school age. However, in developing countries it is not uncommon for adults to present with hypospadias that has not been treated in childhood; herein I report experience of TIP repair in adults.

PATIENTS AND METHODS
TIP urethroplasty was undertaken in 13 adult patients (age range 18–26 years) from December 1999 to January 2004; five had distal penile hypospadias and eight midshaft hypospadias. The patients were selected for TIP urethroplasty only if they had a good urethral plate of reasonable width and had minimal chordee. The hypospadias was repaired under spinal anaesthesia.

The TIP repair was performed as previously described [3,6,7], the salient features being as follows. The penis was degloved and the ventral tethering tissues lateral to the corpus spongiosum and urethral plate excised. A successful urethroplasty was confirmed by an artificial erection, created by an injection with 0.9% saline into the corpora cavernosa of the penis. Tunica albuginea plication was not required in any of the patients. During degloving of the penis special care was taken to create a good gap between the hypospadiac meatus and the degloved skin. This helped in later covering the site of the original meatus completely and thoroughly with the vascularized pedicle.

After dividing the urethral plate in the midline, the neourethra was formed by tubularization of the urethral plates using 5/0 polyglactin on a round-bodied needle using a single-layer running suture. The process of tubularization started proximally from the site of the original meatus and proceeded distally. The following technical aspects were applied during the procedure in all patients: The urethral stent used was a 14 F Nelaton catheter; the urethral plate was tubularized only to the level of the midglans and not to the tip of the glans; the edges of the neomeatus were sutured to the edges of the glans wings using 4/0 chromic catgut; on completing the procedure a stent was taken at the dorsum of the glans and used to fix the stent, to prevent its inadvertent removal. A vascularized pedicle of subcutaneous tissue, harvested from the dorsal hooded prepuse, was brought ventrally to cover the neourethra. Special care was to taken to cover the site of the original meatus completely and thoroughly with the vascularized pedicle.

Antibiotic cover was given for 10 days after surgery, and bladder relaxants, either oxybutynin hydrochloride or tolterodine, were given to all patients for 5 days. The Nelaton catheter was maintained urethrally and connected to a urinary drainage bag, to provide a continuous closed system for drainage. The dressing and the urethral stent were removed after 10 days. No medications were prescribed.
RESULTS

All patients were assessed 10 days after removing the dressing and catheter. They were asked to attend a follow-up assessment at 1, 3, and 6 months, and the meatus was calibrated during these visits using a 16 F catheter. The patients were then asked to attend at 6-monthly intervals. The mean (range) follow-up was 0.5 (0.25–3) years.

A small urinary leak occurred in one patient with distal penile hypospadias, at the site of the original hypospadiac meatus; it stopped spontaneously within a month. None of the patients had meatal stenosis. All the patients voided with a forward and straight urinary stream, and all had a normally situated vertical slit-like meatus. In four patients the meatus looked small but had a normal calibration. They had a good calibre forward urinary stream, with no straining. All the patients were satisfied with the cosmetic result.

DISCUSSION

Historically, >200 procedures have been described for repairing hypospadias. The emphasis of all the modern repairs is not only on creating a neourethra, but also having a good cosmetic result with a normal looking penis. Bracka [8] reported that 72% of young adults felt that a normal appearance was as important a goal as normal function. In the last decade the TIP urethroplasty has gained rapid acceptance, is associated with meatal stenosis in all the present patients; by taking a small stent is used for urethral repair. They had good success in primary repairs, and even when repeat cases are considered, their complication rate was only 18%, which is much less than their overall complication rates, if the native intact urethral plate was used (as in Mathieu, onlay island flap or Thiersch-Duplay repair). Temucin et al. [15] used the TIP repair primarily in five of their patients; they had good results with no complications. Thus repairs using the intact urethral plate are associated with good results even in adults. However, most of the published reports on TIP repair describe it only in children [3,6,7,17–19] and none stressed the results or use of TIP repair in adults.

In the present series TIP urethroplasty gave good results even in adults, but it is important to select the patients appropriately. To be suitable for TIP urethroplasty the hypospadias should basically satisfy two prerequisites, i.e. the presence of a good urethral plate of adequate width and minimum chordee. The absence of a good urethral plate of adequate width and good vascularity is associated with failure. Snodgrass and Lorenzo [20] stated that the contraindications to TIP urethroplasty include previous resection of the urethral plate or obvious scarring of the plate. Thus patients with severe chordee and/or a poor urethral plate, where division or excision of the urethral plate is required, are not candidates for TIP urethroplasty.

Degloving the penis and excising the ventral tethering tissues lateral to the corpus spongiosum and urethral plate, without dividing or dissecting under the urethral plate, corrects the curvature of the penis in most cases. In the present study this was enough to correct chordee in all patients and tunica albuginea plication was not required in any.

Meatal stenosis is one of the complications after TIP urethroplasty, with an incidence of none [3] to 14% [21]. Meatal problems can be the cause of unsatisfactory cosmetic appearance and can cause fistula. In the series reported by Elbakry [22], four of the first seven patients had a fistula and it was associated with meatal stenosis in all. He advocated regular urethral calibration in all patients after TIP urethroplasty; Lorenzo and Snodgrass [23] disagreed with this and felt that regular calibration was not needed.

Adherence to particular technical points resulted in a normally situated vertical slit-like meatus in all the present patients. The tubularization of the urethral plate should end at the level of the midglans and not go to the tip of the glans. The appearance of a properly positioned meatus results more from the closure of the glans wings from the corona to the meatus than from tubularizing the neourethra too far distally; the latter can create obstruction even in the absence of scarring.

In all the present patients the edges of the neourethra were sutured to the edges of the glans wings. This prevents the insinuation of the epithelial edges of the glans wings inside the glans wound, and achieves primary healing between the epithelial edges. Thus, the suturing of the edges of the neourethra to the edges of the glans wings helps not only to give an aesthetically good meatus, but also prevents meatal stenosis. Although there was no meatal stenosis in any of the present patients during the follow-up it is possible that it could develop later.

The urethral stent used was smaller than the neourethra; animal studies confirm that the midline incision through the dorsal aspect of the urethra heals with no fibrosis and by re-epithelialization [24]. The purpose of the stent is to provide urinary drainage; it does not serve as scaffolding around which epithelial growth occurs. This is corroborated in that although stents of 6 F were used in the series by Snodgrass [3], the size of the neourethra was >10 F in all the patients. Steckler and Zaontz [4] also had a low incidence of meatal stenosis or stricture formation, despite using no stents.

The urethral stent was maintained for 10 days in all the present patients; by taking a suture on the dorsal aspect of the glans, the stent was fixed to it, thus preventing its inadvertent removal. As the small stent is held more dorsally it also prevents undue pressure on the ventrally approximated glans wings.
Urethrocuffaneous fistula formation is another complication after repairing hypospadias, but TIP urethroplasty is associated with a low fistula rate. In the present study only one patient had a fistula at the site of the original distal penile hypospadiac meatus after removing the catheter. This closed spontaneously and there was no leak at the 1-month follow-up. One of the key reasons for the low fistula rate with TIP repair is the covering of the neourethra with a layer of the vascular pedicle of subcutaneous tissue harvested from the dorsal prepuce [17]. The spongiosum around the hypospadiac meatus and for some distance proximal to it is very often thin and poorly vascularized. Hence in the patients undergoing onlay island flap or transverse preputial island flap repair, the recommendation is to slit the meatus up to the normal spongiosum [1]. As no such manoeuvre is recommended for TIP urethroplasty, it would be logical to provide good coverage of the area of the hypospadiac meatus with vascularized tissue after tubularizing the urethral plates. Hence, during orthoplasty the penile skin should be degloved to such an extent that the site of the hypospadiac meatus and the thin spongiosum proximal to it are completely exposed. This would help in covering this area with the vascularized pedicle thoroughly and completely.

In conclusion, TIP urethroplasty is associated with good results even in adults; there is no greater incidence of complications than in children. TIP repair uses the intact urethral plate, which has good vascularity and thus helps in achieving good healing, with no greater incidence of infection or fistula. The TIP repair is technically easy and the midline incision over the urethral plate allows tubularization irrespective of the glans configuration. It gives a normal-looking vertical slit-like meatus, so that patients are able to void with a coherent urinary stream. Strict adherence to technical aspects helps to decrease the incidence of meatal problems and fistula formation.

CONFLICT OF INTEREST

None declared.

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Abbreviation: TIP, tubularized incised-plate.
The impact of warm ischaemia on renal function after laparoscopic partial nephrectomy

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OBJECTIVE
To assess the effect of warm ischaemia on renal function after laparoscopic partial nephrectomy (LPN) for tumour, and to evaluate the influence of various risk factors on renal function.

PATIENTS AND METHODS
Data were analysed from 179 patients undergoing LPN for renal tumour under warm ischaemic conditions, with clamping of the renal artery and vein. Renal function was primarily evaluated in two groups of patients: 15 with tumour in a solitary kidney, who were evaluated by serial serum creatinine measurements; and 12 with two functioning kidneys undergoing unilateral LPN, and evaluated by renal scintigraphy before and 1 month after LPN to quantify differential renal function. Also, in all 179 patients, mean serum creatinine data at baseline, 1 day after LPN, at hospital discharge, and at the last follow-up were provided as supportive evidence. Logistic regression analyses were used to assess the effect of various risk factors on renal function after LPN, i.e. patient age, baseline serum creatinine, tumour size, solitary kidney status, duration of warm ischaemia, pelvicalyceal suture repair, urine output and intravenous fluids during LPN.

RESULTS
In the group of patients with a solitary kidney the mean warm ischaemia time was 29 min, kidney parenchyma excised 29%, and serum creatinine at baseline, discharge, the peak after LPN and at the last follow-up (mean 4.8 months) 1.3, 2.3, 2.8, and 1.8 mg/dL, respectively. One patient (6.6%) required temporary dialysis. In the second group, assessed by renal scintigraphy, the function of the operated kidney was reduced by a mean of 29%, commensurate with the amount of parenchyma excised. For all 179 patients, a combination of age ≥70 years and a serum creatinine level after LPN of ≥1.5 mg/dL correlated with a higher serum creatinine after LPN. On logistic regression, baseline serum creatinine and solitary kidney status were the only variables significant for serum creatinine status after LPN.

CONCLUSIONS
The bloodless field provided by renal hilar clamping is important for precise tumour excision, pelvicalyceal suture repair and securing parenchymal haemostasis during LPN. However, renal hilar clamping causes warm ischaemia. These data indicate that the clinical sequelae of warm ischaemic renal injury of ≈30 min are minimal. Advancing age and pre-existing azotaemia increase the...
risk of renal dysfunction after LPN, especially when the warm ischaemia exceeds 30 min.

KEYWORDS
renal tumour, laparoscopy, partial nephrectomy, renal function, nephron-sparing surgery

INTRODUCTION

Laparoscopic partial nephrectomy (LPN) is gaining popularity as a promising minimally invasive nephron-sparing option for treating selected renal tumours [1–3]. Renal hilar clamping during LPN affords the near-bloodless operative field critical for achieving precise tumour excision, watertight pelviccalyceal suture repair and renal parenchymal haemostasis. However, renal hilar clamping causes warm ischaemia (WI), with its attendant potential for ischaemic renal injury.

In the present study we assessed the effect of renal hilar clamping-induced WI on renal function after LPN. Because the presence of a normal contralateral kidney will probably mask significant changes in serum creatinine levels after unilateral LPN, we specifically focused on two groups of patients, i.e. those undergoing LPN for tumour in a solitary kidney, and those with two functioning kidneys undergoing unilateral LPN but in whom radionuclide renal scans before and 1 month after LPN were available for objective documentation of differential renal function. We also examined the serum creatinine database for the entire cohort of 179 patients to identify the effect of various independent risk factors in causing ischaemic renal dysfunction.

PATIENTS AND METHODS

Data were retrospectively analysed from 179 patients undergoing LPN for tumour since August 1999 (mean age 62 years, SD 13, range 23–87); the mean (SD) American Society of Anesthesiology score was 2.6 (0.6, 1–4), the body mass index 30.1 (7.9, 18–74) kg/m2, and tumour size 2.9 (1.3, 1–10) cm. The technique of LPN was detailed elsewhere [1]. Specifically, LPN routinely used WI, with the renal artery and vein clamped in all 179 patients. The mean WI time was 31 (10, 4–55) min (Fig. 1), the operative duration 198 (90–345) min, and the estimated blood loss 216 (25–1500) mL immediately on concluding the operation, after consultation with the assistants, the operating surgeon documented the consensus subjective impression of the percentage of kidney parenchyma excised during the LPN. Baseline and perioperative data were collected and entered prospectively into a computerized database. Follow-up serum creatinine and MAG3 renal scan data were collected by telephone contact with the patient and/or local physician.

Fifteen patients had a LPN for tumour in a solitary kidney; their serum creatinine levels (normal 0.7–1.4 mg/dL) were available serially before LPN, at hospital discharge, at the peak recorded after LPN, and at the last follow-up. In 12 further patients undergoing unilateral LPN with both kidneys functioning, 99mTc-MAG3 renal scintigrams were available before and 1 month after LPN, to quantify any change in differential renal function. These two subgroups were used as the primary determinants for assessing renal function after LPN.

Also, for the entire study population of 179 patients, serum creatinine levels at baseline (before LPN), 1 day after LPN, at discharge and at the last follow-up were assessed as supporting evidence of renal functional status. For further analysis, all 179 patients were stratified in three different ways. First, based on WI time, patients were divided into two groups (group 1, WI < 30 min, group 2, ≥30 min); second, based on WI and age, patients were divided into four groups (group A1, WI < 30 min and <70 years old, group A2, WI < 30 min and age ≥70; group B1, WI ≥30 min and age ≤70; and group B2, WI ≥30 min and age ≥70). Third, based on WI and baseline serum creatinine level, patients were divided into four groups (group C1, WI < 30 min and serum creatinine <1.5 mg/dL; group C2, WI < 30 min and creatinine ≥1.5 mg/dL; group D1, WI ≥30 min and creatinine <1.5 mg/dL; and group D2, WI ≥ 30 min and creatinine ≥1.5 mg/dL).

The statistical significance between various groups was assessed using the t-test, Wilcoxon rank-sum test, ANOVA, or Kruskal-Wallis test for continuous variables, and the chi-square test for categorical variables. All data are reported as the mean/median (SD/range), with P < 0.05 considered to indicate statistically significant differences. Multiple linear regression analysis was used to assess the effect of various independent variables on serum creatinine after surgery, i.e. patient age, WI time, pelviccalyceal suture repair, tumour size, baseline serum creatinine, solitary kidney status, and intravenous fluid administration and urine output during LPN.

RESULTS

No kidney was lost because of ischaemic sequelae. The details for the 15 patients undergoing LPN for tumour in a solitary kidney are shown in Table 1; one patient with a 6.5-cm tumour in the solitary kidney had a 60% heminephrectomy and then required temporary haemodialysis. No other patient required haemodialysis after LPN.

The details of the 12 patients who had MAG3 renal scintigraphy before and after LPN to assess differential renal function are shown in Table 2. The mean differential function of the target kidney was 45% before and 32% 1 month after LPN; as such, the calculated reduction of function of the operated kidney from baseline was 29%.

Patients in group 1 (WI < 30 min) had a shorter operating time, less blood loss, a lower incidence of pelviccalyceal entry and a shorter hospital stay than those in group 2 (WI ≥ 30 min; Table 3). Nevertheless, groups 1
and 2 were comparable in terms of serum creatinine 1 day after LPN, at discharge, and at the latest follow-up. The mean follow-up in group 1 was longer than in group 2 (Table 3).

Compared with group A1 (WI < 30 min and age < 70 years) patients in group A2 (WI < 30 min and age ≥ 70 years) had a higher serum creatinine 1 day after LPN, at discharge and at the latest follow-up (Table 4). Similarly, compared with group A1, patients in B2 had a higher serum creatinine 1 day after LPN, at discharge, and at the last follow-up, and a higher percentage increase from baseline. Both groups with a higher baseline serum creatinine (Groups C2 and D2) had a significantly higher serum creatinine level than the groups C1 and D1 (normal baseline creatinine) at each time assessed. However, there was no difference in serum creatinine between groups C2 and D2 1 day after LPN, at discharge or at the latest follow-up (Table 4).
levels after LPN (Table 5). A high baseline serum creatinine was predictive of creatinine at 1 day after LPN, at discharge and at the last follow-up (all $P < 0.001$; Table 5). Although solitary kidney status correlated with maximum serum creatinine ($P < 0.001$), it did not correlate with serum creatinine at the last follow-up. All other evaluated factors did not correlate with postoperative serum creatinine levels at any time (Table 5).

**DISCUSSION**

LPN is gaining popularity as a viable minimally invasive treatment option for selected patients with a renal tumour [1–3]. We attempted to simulate the time-tested surgical principles of open PN in our technique of LPN [1,4], central to which is the routine clamping of the renal artery and vein. The near-bloodless field with clear visibility offered by renal hilar clamping provides an optimal surgical environment for precise tumour excision, watertight suture repair of the pelvicalyceal system, and haemostatic suture repair of the soft unperfused renal parenchyma. Obviously, renal hilar control is of even greater significance for excising larger central tumours abutting or infiltrating the renal sinus. However, clamping the renal hilum is associated with the potential for ischaemic renal damage; it is therefore important to evaluate the impact of WI on renal function.

Canine studies show that recovery of the unprotected kidney depends on the period of WI [5,6]. Recovery of renal function is complete within minutes after 10 min of WI, complete within hours after 20 min, complete within 3–9 days after 30 min, usually complete within weeks after 60 min, and incomplete (30–50%) after 120 min [5,6]. As such, current clinical practice is to limit the WI time to ≈30 min. At our institute, renal hypothermia is necessary infrequently, in only ≈5% of patients, even during open PN [4].

The mean (range) WI time in the present study was 31 (4–55) min; the data show the technical feasibility of reliably performing all the critical steps of precise tumour excision and haemostatic renal reconstruction in a time-sensitive fashion, using a purely laparoscopic technique. In our recent comparison of open and LPN in 200 patients [4], the mean WI time was significantly longer in the laparoscopic than in the open group (28 vs 18 min, $P < 0.001$) but the median serum creatinine before (both 1.0 mg/dL) and after surgery (1.0 vs 1.1 mg/dL) was similar in the two groups.

Measuring serum creatinine in patients with a solitary kidney provides an accurate assessment of postoperative renal function in the clinical setting. Serial serum creatinine data were analysed in 15 patients undergoing LPN for tumour in a solitary kidney; the mean tumour size was 3.5 cm, WI time 29 min and percentage kidney excised 29%. There was a significant rise in serum creatinine

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 (WI &lt; 30 min)</td>
<td>2 (WI ≥ 30 min)</td>
</tr>
<tr>
<td>No. of patients</td>
<td>74</td>
<td>105</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>40 (54)</td>
<td>65 (62)</td>
</tr>
<tr>
<td>Mean (sd, range):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>age, years</td>
<td>64 (13, 23–87)</td>
<td>60 (13, 30–86)</td>
</tr>
<tr>
<td>ASA class</td>
<td>2.7 (0.6, 2–4)</td>
<td>2.5 (0.6, 1–4)</td>
</tr>
<tr>
<td>body mass index, kg/m²</td>
<td>29.8 (8.0, 18–59)</td>
<td>30.2 (7.8, 18–74)</td>
</tr>
<tr>
<td>tumour size, cm</td>
<td>2.8 (1.4, 0.9–10)</td>
<td>3.1 (1.3, 1.0–8.3)</td>
</tr>
<tr>
<td>Central tumours, n (%)</td>
<td>18 (31)</td>
<td>26 (33)</td>
</tr>
<tr>
<td>Calyceal entry and repair, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>before LPN</td>
<td>1.2 (0.5, 0.6–3.4)</td>
<td>1.1 (0.5, 0.4–3.1)</td>
</tr>
<tr>
<td>1 day after</td>
<td>1.2 (0.5, 0.6–2.9)</td>
<td>1.4 (0.5, 0.5–3.7)</td>
</tr>
<tr>
<td>at discharge</td>
<td>1.3 (0.7, 0.6–4.2)</td>
<td>1.4 (0.6, 0.5–4.0)</td>
</tr>
<tr>
<td>at last follow-up</td>
<td>1.3 (0.6, 0.5–4.2)</td>
<td>1.3 (0.6, 0.5–3.7)</td>
</tr>
<tr>
<td>maximum</td>
<td>1.5 (0.7, 0.6–4.2)</td>
<td>1.6 (1.0, 0.7–8.7)</td>
</tr>
<tr>
<td>Duration to last estimate, months</td>
<td>6.1 (7.7, 0.03–27)</td>
<td>2.6 (3.8, 0.03–18)</td>
</tr>
<tr>
<td>% increase at last follow-up</td>
<td>13.2 (21.4, 0–50)</td>
<td>15.5 (32, 0–170)</td>
</tr>
<tr>
<td>No. patients requiring dialysis</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

*Student’s t-test; †chi-square test; ‡Wilcoxon rank-sum test; ¶% of preoperative value. ASA, American Society of Anesthesiology.
immediately after LPN, reflecting some acute tubular necrosis from the WI, but it reverted to baseline with time. Thus, in these 15 patients, within the confines of the WI (29 min), the nadir serum creatinine was commensurate with the approximate amount of renal parenchyma excised.

The 12 patients assessed by renal scans (Table 2) had a mean 29% reduction in differential renal function (45% before and 32% after LPN), which generally corresponded to the percentage of kidney parenchyma excised (29%).

As expected, in the presence of both functioning kidneys, unilateral LPN did not significantly affect serum creatinine levels. Specifically comparing group 1 and group 2, there was no significant difference in serum creatinine level at any time (Table 3). The significance of these data may be somewhat diminished by the presence of a functioning contralateral kidney, status of hydration, exposure to nephrotoxins and muscle mass.

WI is incrementally deleterious to renal function [5,6]; moreover, these deleterious effects may be compounded by increasing age and high baseline serum creatinine level. As such, we have always tried to minimize the duration of WI during LPN. We interpret the influence of WI stratified by age or baseline serum creatinine (Table 4) as follows. There was no difference in mean serum creatinine at various times after LPN between groups A1 and B1, or between A2 and B2; similarly there was no difference between C1 and D1, and C2 and D2. Taken together, these group comparisons essentially compare patients of similar age (A1 vs B1, A2 vs B2), or similar baseline serum creatinine (C1 vs D1, C2 vs D2), separated by an arbitrary WI threshold of 30 min. Given that most of the WI times were <30 min, and that 92% of the patients had two functioning kidneys, it is not surprising that there were no significant differences in mean serum creatinine levels. However, there were significant differences in serum creatinine after LPN when comparing the extreme groups, i.e. A1 vs B2 and C1 vs D2. Thus, patients with a WI of <30 min and aged <70 years or a baseline serum creatinine of <1.5 mg/dL had significantly lower mean serum creatinine levels at all times than had patients with a WI of ≥30 min and aged ≥70 years or a baseline serum creatinine of ≥1.5 mg/dL. This rise in serum creatinine was more pronounced soon after LPN and typically tended towards baseline at the subsequent follow-up. More telling is that these differences in serum creatinine were significant despite the presence of a

### Table 4: LPN; the effect of WI and age on serum creatinine levels

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>A (WI &lt; 30 min)</th>
<th>B (WI ≥ 30 min)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subgroup (age, years)</td>
<td></td>
<td>A1 (&lt;70)</td>
<td>A2 (≥70)</td>
<td>B1 (&lt;70)</td>
</tr>
<tr>
<td>No. of patients</td>
<td></td>
<td>47</td>
<td>27</td>
<td>72</td>
</tr>
<tr>
<td>Mean (range):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WI time, min</td>
<td></td>
<td>22 (4–29)</td>
<td>22 (10–29)</td>
<td>37 (30–55)</td>
</tr>
<tr>
<td>age, years</td>
<td></td>
<td>56 (23–69)</td>
<td>76 (70–87)</td>
<td>53 (30–69)</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL before LPN</td>
<td></td>
<td>1.1 (0.6–2.6)</td>
<td>1.3 (0.6–3.4)</td>
<td>1.0 (0.4–2.6)</td>
</tr>
<tr>
<td>1 day after</td>
<td></td>
<td>1.1 (0.6–2.8)</td>
<td>1.5 (0.6–2.9)</td>
<td>1.3 (0.5–3.2)</td>
</tr>
<tr>
<td>at discharge</td>
<td></td>
<td>1.2 (0.6–3.6)</td>
<td>1.6 (0.6–4.2)</td>
<td>1.4 (0.5–3.4)</td>
</tr>
<tr>
<td>at last follow-up</td>
<td></td>
<td>1.2 (0.6–2.9)</td>
<td>1.5 (0.5–4.2)</td>
<td>1.2 (0.5–2.8)</td>
</tr>
<tr>
<td>time to last follow-up, months</td>
<td></td>
<td>6.2 (0.03–27)</td>
<td>6.0 (0.03–24)</td>
<td>2.3 (0.03–18)</td>
</tr>
<tr>
<td>% increase at last follow-up†</td>
<td></td>
<td>11.4 (0–50)</td>
<td>16.3 (0–50)</td>
<td>22.9 (0–100)</td>
</tr>
<tr>
<td>Subgroup (creatinine, mg/dL‡)</td>
<td></td>
<td>C1 (&lt;1.5)</td>
<td>C2 (≥1.5)</td>
<td>D1 (&lt;1.5)</td>
</tr>
<tr>
<td>No. of patients</td>
<td></td>
<td>60</td>
<td>14</td>
<td>93</td>
</tr>
<tr>
<td>Mean (range):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WI time, min</td>
<td></td>
<td>22 (4–29)</td>
<td>23 (10–29)</td>
<td>37 (30–55)</td>
</tr>
<tr>
<td>age, years</td>
<td></td>
<td>62 (23–86)</td>
<td>70 (50–87)</td>
<td>60 (30–88)</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL before LPN</td>
<td></td>
<td>0.9 (0.6–1.4)</td>
<td>2.0 (1.5–3.4)</td>
<td>1.0 (0.4–1.4)</td>
</tr>
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<td>1 day after</td>
<td></td>
<td>1.1 (0.6–2.4)</td>
<td>1.9 (1.2–2.9)</td>
<td>1.2 (0.5–2.5)</td>
</tr>
<tr>
<td>at discharge</td>
<td></td>
<td>1.1 (0.6–3.6)</td>
<td>2.1 (0.9–4.2)</td>
<td>1.2 (0.5–3.4)</td>
</tr>
<tr>
<td>at last follow-up</td>
<td></td>
<td>1.1 (0.5–1.9)</td>
<td>2.3 (1.4–4.2)</td>
<td>1.2 (0.5–3.3)</td>
</tr>
<tr>
<td>time to last follow-up, months</td>
<td></td>
<td>6.0 (0.03–27)</td>
<td>6.6 (0.03–20)</td>
<td>2.5 (0.03–18)</td>
</tr>
<tr>
<td>% increase at last follow-up†</td>
<td></td>
<td>13 (0–50)</td>
<td>14.1 (0–44.4)</td>
<td>26.9 (0–170)</td>
</tr>
<tr>
<td>No. patients requiring dialysis</td>
<td></td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
| P values: for subgroups A,B: A, A1 vs A2; B, A1 vs B1; C, A1 vs B2; D, A2 vs B1; E, A2 vs B2; F, B1 vs B2. For subgroups C and D, A, C1 vs C2; B, C1 vs D1; C, C1 vs D2; D, C2 vs D1; E, C2 vs D2; F, D1 vs D2.  †% of preoperative value.  ‡Baseline serum creatinine before LPN.
functioning contralateral kidney. We interpret these findings to suggest that prolonged WI is not tolerated well by the compromised kidney. Indeed, had these calculations been for a sufficiently large series of patients with a solitary kidney, or using more sensitive indicators of renal injury, we think it is likely that the differences would have been more significant.

Logistic linear regression analysis showed that only the baseline serum creatinine level was predictive of a high level after LPN. Solitary kidney status was predictive of a higher maximum recorded serum creatinine, but not of serum creatinine at the last follow-up. All other factors did not correlate significantly with postoperative serum creatinine.

In selected patients in whom an extended period of renal hilar clamping is anticipated to complete the LPN, renal hypothermia can now be achieved by minimally invasive means. Recently, three different techniques of laparoscopic renal hypothermia were described; surface hypothermia with ice slush [7], retrograde cooling of the collecting system with cold perfusion [8], and intra-arterial cooling through a percutaneously placed angiocatheter [9]. In these limited initial clinical experiences described, the core renal temperatures achieved by these various techniques were as follows 5–19 °C (surface-contact ice-slush), 24 °C (transureteric cold perfusion) and 25 °C (intra-arterial). Further refinement of and experience with these techniques is necessary before wider clinical use.

Renal hilar clamping during LPN is not used universally; recently, Guillonneau et al. [10] retrospectively compared LPN with (12 patients) or without (16) renal hilar clamping. The tumours were larger in the first group (1.9 vs 2.5 cm). LPN with no renal hilar clamping was associated with a significantly greater blood loss (708 vs 270 ml, \( P = 0.014 \)), and longer surgery (179 vs 121 min, \( P = 0.004 \)) than with renal hilar control. There was no significant difference in postoperative serum creatinine level (1.3 vs 1.45 mg/dL, \( P = 0.075 \)) between the groups.

The drawbacks of the present study include its retrospective design; there were also relatively few patients with a solitary kidney or with renal scan data before and after LPN. Although the amount of parenchyma excised was determined prospectively by consensus among the surgeons during LPN, it remains inherently a subjective estimate. Finally, serum creatinine is a relatively less sensitive indicator of renal functional compromise. Future studies should include creatinine clearance data accrued prospectively.

In conclusion, a substantive LPN typically requires renal hilar control; its many technical advantages notwithstanding, renal hilar clamping causes some WI. In patients with a solitary kidney, within the confines of the present WI, there was no significant renal damage and the nadir serum creatinine after surgery appeared commensurate with the approximate amount of kidney parenchyma excised. These findings were objectively corroborated by differential renal function on MAG3 scans before and 1 month after LPN.

The present data suggest that the clinical sequelae of WI injury of >30 min are minimal. Advancing age and pre-existing renal insufficiency appear to be associated with greater ischaemic renal dysfunction, especially when the duration of WI is >30 min.

**CONFLICT OF INTEREST**

Inderbir Gill is a speaker for Pfizer and an investigator for Baxter.

**REFERENCES**


**TABLE 5** Factors affecting serum creatinine: multivariate analysis

<table>
<thead>
<tr>
<th>Factor</th>
<th>P for serum creatinine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>at discharge</td>
</tr>
<tr>
<td>WI</td>
<td>0.51</td>
</tr>
<tr>
<td>Age</td>
<td>0.39</td>
</tr>
<tr>
<td>Serum creatinine before LPN</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Solitary kidney status</td>
<td>0.67</td>
</tr>
<tr>
<td>Presence of calyceal entry</td>
<td>0.47</td>
</tr>
<tr>
<td>Tumour size</td>
<td>0.38</td>
</tr>
<tr>
<td>Intraoperative urine output</td>
<td>0.16</td>
</tr>
<tr>
<td>Intraoperative intravenous fluids</td>
<td>0.50</td>
</tr>
</tbody>
</table>

* statistically significant.
Laparoscopic ice slush renal hypothermia for partial nephrectomy: the initial experience. *J Urol* 2003; **170**: 52–6


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Abbreviations: L(PN), laparoscopic (partial nephrectomy); WI, warm ischaemia.
Alteration of body configuration after retroperitoneoscopic nephrectomy and nephroureterectomy

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Accepted for publication 29 July 2004

OBJECTIVE
To evaluate objective alterations of body configuration in patients who treated with retroperitoneoscopic nephrectomy (RN) and retroperitoneoscopy-assisted nephrectomy (RAN).

PATIENTS AND METHODS
Twenty-six patients who had RN and 23 RAN were eligible for the study. Abdominal computed tomography films before and after surgery were evaluated. The intra-abdominal content surrounded by the vertebral bones and the muscles forming the trunk of the body were divided into four subspaces. The areas of these four portions were measured, and the ratio of occupation of each portion calculated before compared with that obtained after surgery.

RESULTS
While RAN had little impact on body configuration, RN significantly affected it; after RN the total area and area of ventral subspaces decreased homogeneously throughout the L2–L4 levels. The ipsilateral dorsal subspace had a marked cranial decrease in area and no caudal alteration.

CONCLUSIONS
While RAN has little effect on body configuration, RN has a significant effect, as measured objectively. Continuing the skin incision between ports and muscle splitting to extract the specimen is probably responsible for the difference between the findings of RAN and RN.

KEYWORDS
body configuration, nephrectomy, nephroureterectomy, retroperitoneoscopy, CT

INTRODUCTION
Retroperitoneal procedures via a flank incision are often used in urological surgery for renal, ureteric and adrenal disease. Despite using the sophisticated technique introduced by Riehle et al. [1], many patients complain of a change in their body image after urological surgery via this approach [2,3]. We reported previously that urological renal surgery via an 11th rib transcostal incision significantly increased the ratio of the ipsilateral portion from the L2 to L4 levels, mainly as a result of 'posterolateral bulging', and that this objective change in body configuration also represented the patients' perception of the change in body image [2].

Recently, the transperitoneal and retroperitoneal laparoscopic approaches for renal surgery have been increasingly used worldwide, because of their low invasiveness. Here, we determined the degree of alteration in body configuration in patients who had retroperitoneoscopic renal surgery.

PATIENTS AND METHODS
From January 1999 to September 2002, 27 patients had retroperitoneoscopic nephrectomy (RN) and 23 retroperitoneoscopy-assisted nephrectomy (RAN). One patient treated by RN was excluded from the study because there was no abdominal CT before surgery; all the remaining patients were eligible and their characteristics are shown in Table 1.

To evaluate changes in body configuration, abdominal CT films taken before and after surgery were assessed. The techniques of RN and RAN are described elsewhere [4,5]. Briefly, for RN, a purely endoscopic isolation of the kidney from adjacent structures, using three trocars, was followed by manual removal of the specimen via an incision, which was made by continuing the skin incision between trocar sites and muscle splitting. For RAN, a purely endoscopic isolation of the kidney and the upper portion of the ureter, as in RN, was followed by dissecting the lower portion of the ureter, excising the ureter with a small bladder cuff, repairing the bladder, and enucleating the specimen via an 8-cm pararectal or midline incision.

To measure the intra-abdominal content (IAC), abdominal CT films were taken a median (range) of 8 (6–38) months after surgery in the RN group, and at 10 (6–23) months in the RAN group. Although CT of three patients who had surgery before 2000 was retrospective, CT of the other 47 was prospective, and at least 6 months after surgery. The detailed method of measuring the IAC using abdominal CT was described previously [2]. Briefly, nine slices from the L2 to L4 level were selected for measurement in each CT film. The area on a slice which was surrounded by the bones and the muscle tissues forming the abdominal trunk was defined as the IAC. This area was divided into four subspaces, as shown in Fig. 1. The areas of these subspaces were measured using image analysis software (NIH version 1.62). The mean of the three measurements for each vertebral level were analysed using the paired Student's t-test, with P<0.05 considered to indicate significant differences.
RESULTS

The total areas of IAC did not differ significantly after RAN, but were, at each level, significantly lower after RN (Table 2). Before surgery, the area of the right half of the IAC was nearly equal to that of the left half in both groups, and the area of the ipsilateral half was nearly equal to that of the contralateral half in the RAN group (data not shown). However, at L2 level, the area of the ipsilateral half before surgery was significantly larger than that of the contralateral half in the RN group (data not shown). In the RAN group, the crude area of each of the four subspaces did not change significantly after surgery, with a few exceptions (Table 3). In this group, the ratio of occupation of every subspace did not change either (Table 4).

Conversely, the crude area of many portions of the subspaces significantly decreased after RN (Table 3). In the ipsilateral-ventral and contralateral-ventral portions there was a slight but significant reduction of area ($P = 0.010$–$0.044$) homogeneously through all levels. In the ipsilateral-dorsal portion, there was a very significant reduction of area ($P = 0.003$ to $< 0.001$) from upper-L2 to mid-L3 levels, although there was no such reduction at the L4 level. Generally there was no change in area in the contralateral-dorsal portion. In the RN group, the ratios of occupation of some subspaces also changed significantly after surgery (Table 4). The occupying ratio of ipsilateral to total area and that of ipsilateral-dorsal to dorsal area were significantly lower at the L2 and L3 levels. No other ratios, including those of dorsal (ventral) to total, ipsilateral-ventral (contralateral-ventral) to ventral, ipsilateral-dorsal (ipsilateral-ventral) to ipsilateral, and contralatero-dorsal (contralatero-ventral) to contralateral area, changed significantly after surgery.

Although objective measurements of the area showed marked changes after RN at more cranial levels, the appearance of muscle layers was altered at caudal levels. Two typical patterns of CT images before and after surgery at upper-L4 level of RN patients are shown in Fig. 2a,b. One pattern is a defect of inner muscle layers (transverse abdominis and internal oblique abdominis muscles in this patient) with no bulging of the abdominal wall. The other is the blurring and swelling of the lateral abdominal muscle layers.

DISCUSSION

Laparoscopic nephrectomy and nephroureterectomy are generally considered less invasive than open procedures. Several surgeons have reported that transperitoneal and retroperitoneal nephrectomy resulted in lower blood loss, hospital stay, analgesic requirements and convalescence than open nephrectomy [6–8]. Hsu et al. [9] reported similar findings in patients aged $\geq 80$ years. Fornara et al. [10] reported that laparoscopic renal operations resulted in lower serum levels of C-reactive protein and interleukin–6 than open renal operations. Although there are fewer reports of decreased invasiveness of laparoscopic nephroureterectomy than laparoscopic nephrectomy, our previous analysis also showed that RAN resulted in less blood loss and shorter convalescence than open nephroureterectomy.

The present study assessed the invasiveness of RN and RAN from a cosmetic perspective. Objective analyses using measurements of the area of IAC showed that RAN had almost no

---

TABLE 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>RN</th>
<th>RAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) age, years</td>
<td>66.2 (11.4)</td>
<td>72.8 (7.1)</td>
</tr>
<tr>
<td>Male</td>
<td>20</td>
<td>16</td>
</tr>
<tr>
<td>Female</td>
<td>6</td>
<td>7</td>
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<tr>
<td>Laterality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Left</td>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td>Disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal cancer</td>
<td>25</td>
<td>–</td>
</tr>
<tr>
<td>Renal pelvic cancer</td>
<td>–</td>
<td>7</td>
</tr>
<tr>
<td>Ureteric cancer</td>
<td>–</td>
<td>7</td>
</tr>
<tr>
<td>Renal pelvic/ureteric</td>
<td>–</td>
<td>8</td>
</tr>
<tr>
<td>others</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

FIG. 1. Measurement of the IAC. a, abdominal CT; b, a thick black line surrounds the area of IAC; c, three circles indicate the tip of the spinal process (red), the centre of the spinal canal (yellow), and the centre of the white line (blue), respectively. The asterisk is the dorsal centre of the IAC, which is determined as the intersection of a line through the tip of the spinal process, the centre of the spinal cord (dashed line) and the margin of the vertebral body; d, The red line makes a right angle with the dashed line. The red and blue lines divide the IAC into four subspaces.
effect on body configuration. This finding suggests that three small wounds for trocars do not influence the configuration of the body trunk, although these wounds penetrate three muscle layers of the full-thickness of the lateral abdomen. Conversely, RN had a major effect on body configuration; the characteristics of this change after RN included: (i) significant reduction of the crude area of IAC from L2 to L4; (ii) homogeneously reduced area of ventral subspaces from L2 to L4; (iii) a marked reduction of area cranially and no alteration caudally in the ipsilatero-dorsal portion; (iv) no change in the area of the contralatero-dorsal subspace; and (v) reduced ratio of occupation of the ipsilatero-dorsal subspace to total area in the cranial portion. It is obvious that continuing the skin incision between ports and muscle splitting to extract a specimen is responsible for the difference between the effects of RAN and RN. The effect of RN in this study suggest that it induces a reverse direction of deviation of the IAC cranially compared with renal surgery via the trans-11th rib approach, which results in deviation of the IAC in the ipsilatero-dorsal direction [2]. The decrease of IAC after RN may have resulted from scarring and contracture of muscle layers, which would be overcome by ‘posterolateral bulging’, induced by atrophy of the muscle layers after a conventional flank incision [2]. However, CT of the cranial level after surgery showed no morphological differences from that beforehand, which accounted for the reduction of area. Rather, CT after surgery of the caudal level showed small defects of the inner muscle layers, or blurring and swelling of all three muscle layers of the lateral abdominal trunk. Thus, we can find no clear reason for this discrepancy. Creating other wounds for specimen extraction, including a lower midline and Gibson incision, would influence body configuration in other ways.

The subjective perception of patients of changes in body image is a very important issue. As no validated questionnaire on patients’ perception of altered body image is presently available, we cannot examine this issue. Although this study of body configuration used CT with the patient supine, patients perceive their cosmetic change while sitting or standing. Thus, the CT results may not accurately reflect patients’ perceptions. This is one of the limitations of the study; another is that although CT was used ≥6 months after surgery, the follow-up was relatively short. Thus, body configuration and patient perception of body alterations might change with a longer follow-up.

The CT technique can detect smaller differences in body configuration than can be perceived by patients. In the future, this technique may be applied to other conditions, e.g. muscle atrophy and/or scarring after surgery or similar conditions.

ACKNOWLEDGEMENT

We thank Drs Noriaki Utsunomiya, Hiroki Ohara, Nobufumi Ueda, and Naoki Terada for their cooperation with this study.

CONFLICT OF INTEREST

None declared.
### TABLE 3 Areas (cm²) of subspaces of the IAC

<table>
<thead>
<tr>
<th>Operation/level</th>
<th>Ipsilatero-ventral before</th>
<th>Ipsilatero-ventral after</th>
<th>Contralatero-ventral before</th>
<th>Contralatero-ventral after</th>
</tr>
</thead>
<tbody>
<tr>
<td>RN</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>upper-L2</td>
<td>97.0 (33.6)</td>
<td>88.4 (25.7)*</td>
<td>97.7 (34.0)</td>
<td>89.5 (25.1)*</td>
</tr>
<tr>
<td>mid- L2</td>
<td>91.1 (35.3)</td>
<td>80.1 (27.6)*</td>
<td>91.8 (36.4)</td>
<td>81.7 (27.9)*</td>
</tr>
<tr>
<td>lower-L2</td>
<td>81.6 (35.9)</td>
<td>70.6 (28.1)*</td>
<td>82.2 (36.4)</td>
<td>72.3 (27.1)*</td>
</tr>
<tr>
<td>upper-L3</td>
<td>75.0 (35.3)</td>
<td>63.7 (27.0)*</td>
<td>76.8 (35.9)</td>
<td>66.0 (26.0)*</td>
</tr>
<tr>
<td>mid-L3</td>
<td>71.2 (34.4)</td>
<td>60.0 (26.8)*</td>
<td>72.9 (34.8)</td>
<td>62.2 (25.4)*</td>
</tr>
<tr>
<td>lower-L3</td>
<td>67.3 (32.8)</td>
<td>54.3 (26.4)*</td>
<td>68.3 (33.0)</td>
<td>55.6 (26.1)*</td>
</tr>
<tr>
<td>upper-L4</td>
<td>63.7 (32.8)</td>
<td>50.8 (24.7)†</td>
<td>64.1 (32.5)</td>
<td>51.1 (24.3)*</td>
</tr>
<tr>
<td>mid-L4</td>
<td>63.4 (32.1)</td>
<td>51.9 (25.0)*†</td>
<td>63.9 (32.0)</td>
<td>50.5 (23.4)*</td>
</tr>
<tr>
<td>lower-L4</td>
<td>67.1 (31.6)</td>
<td>52.9 (28.4)*</td>
<td>67.5 (31.5)</td>
<td>51.0 (23.4)*†</td>
</tr>
<tr>
<td>L2 (mean)</td>
<td>89.9 (34.6)</td>
<td>79.7 (26.9)*</td>
<td>90.6 (35.4)</td>
<td>81.2 (26.5)*</td>
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<tr>
<td>L3 (mean)</td>
<td>72.9 (34.0)</td>
<td>56.4 (26.4)*</td>
<td>72.7 (34.4)</td>
<td>61.3 (25.6)*</td>
</tr>
<tr>
<td>L4 (mean)</td>
<td>63.4 (32.1)</td>
<td>52.0 (25.2)*</td>
<td>63.7 (31.5)</td>
<td>51.0 (23.4)*</td>
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<tr>
<td>RAN</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>upper-L2</td>
<td>92.0 (25.7)</td>
<td>92.8 (24.5)</td>
<td>93.1 (26.6)</td>
<td>94.2 (27.2)</td>
</tr>
<tr>
<td>mid- L2</td>
<td>83.5 (26.8)</td>
<td>85.6 (27.0)</td>
<td>85.7 (27.8)</td>
<td>86.3 (28.9)</td>
</tr>
<tr>
<td>lower-L2</td>
<td>74.8 (24.0)</td>
<td>76.0 (27.2)</td>
<td>75.4 (29.1)</td>
<td>77.6 (29.2)</td>
</tr>
<tr>
<td>upper-L3</td>
<td>68.2 (29.9)</td>
<td>70.8 (27.6)</td>
<td>68.4 (29.4)</td>
<td>69.6 (28.2)</td>
</tr>
<tr>
<td>mid-L3</td>
<td>64.1 (31.3)</td>
<td>63.9 (26.6)</td>
<td>65.4 (31.0)</td>
<td>65.0 (29.3)</td>
</tr>
<tr>
<td>lower-L3</td>
<td>57.9 (30.7)</td>
<td>56.9 (28.9)</td>
<td>59.4 (31.1)</td>
<td>60.0 (29.2)</td>
</tr>
<tr>
<td>upper-L4</td>
<td>54.3 (28.6)</td>
<td>57.2 (28.1)</td>
<td>54.5 (29.0)</td>
<td>56.9 (27.7)</td>
</tr>
<tr>
<td>mid-L4</td>
<td>54.3 (26.6)</td>
<td>57.3 (28.0)</td>
<td>54.9 (27.7)</td>
<td>56.3 (25.4)</td>
</tr>
<tr>
<td>lower-L4</td>
<td>53.0 (24.9)</td>
<td>55.5 (25.6)</td>
<td>53.9 (24.1)</td>
<td>55.8 (25.3)</td>
</tr>
<tr>
<td>L2 (mean)</td>
<td>83.3 (26.5)</td>
<td>84.8 (25.9)</td>
<td>84.7 (27.6)</td>
<td>86.0 (26.2)</td>
</tr>
<tr>
<td>L3 (mean)</td>
<td>63.4 (30.4)</td>
<td>63.9 (28.2)</td>
<td>64.7 (30.2)</td>
<td>64.9 (28.7)</td>
</tr>
<tr>
<td>L4 (mean)</td>
<td>53.9 (26.6)</td>
<td>56.7 (27.1)</td>
<td>54.5 (26.8)</td>
<td>56.3 (26.0)</td>
</tr>
</tbody>
</table>

*P < 0.05, †P < 0.01 and ‡P < 0.001.

### TABLE 4 Ratios (%) of the distribution of subspaces

<table>
<thead>
<tr>
<th>Level</th>
<th>RN before</th>
<th>RN after</th>
<th>LPS before</th>
<th>LPS after</th>
</tr>
</thead>
<tbody>
<tr>
<td>upper-L2</td>
<td>51.0 (1.9)†</td>
<td>50.1 (1.8)*</td>
<td>52.8 (6.1)</td>
<td>50.9 (6.2)*</td>
</tr>
<tr>
<td>mid- L2</td>
<td>51.0 (1.9)†</td>
<td>50.0 (1.9)*</td>
<td>53.2 (5.3)</td>
<td>50.9 (5.9)*</td>
</tr>
<tr>
<td>lower-L2</td>
<td>51.0 (2.2)*</td>
<td>50.1 (2.3)*</td>
<td>52.7 (5.5)</td>
<td>51.3 (6.4)</td>
</tr>
<tr>
<td>upper-L3</td>
<td>50.9 (2.3)*</td>
<td>49.8 (2.8)*</td>
<td>53.5 (6.5)</td>
<td>51.2 (6.8)*</td>
</tr>
<tr>
<td>mid-L3</td>
<td>50.7 (2.1)*</td>
<td>49.5 (3.3)*</td>
<td>53.2 (7.2)</td>
<td>50.7 (7.6)*</td>
</tr>
<tr>
<td>lower-L3</td>
<td>50.6 (2.4)*</td>
<td>49.6 (3.6)*</td>
<td>52.3 (6.9)</td>
<td>50.5 (7.9)*</td>
</tr>
<tr>
<td>upper-L4</td>
<td>50.1 (2.2)*</td>
<td>49.9 (2.9)</td>
<td>50.7 (6.7)</td>
<td>50.0 (6.5)</td>
</tr>
<tr>
<td>mid-L4</td>
<td>50.0 (2.2)*</td>
<td>49.9 (3.0)</td>
<td>50.8 (6.8)</td>
<td>49.2 (7.2)</td>
</tr>
<tr>
<td>lower-L4</td>
<td>49.6 (2.5)*</td>
<td>49.7 (3.5)</td>
<td>49.6 (7.8)</td>
<td>49.2 (8.2)</td>
</tr>
<tr>
<td>L2 (average)</td>
<td>51.0 (1.9)</td>
<td>50.0 (1.9)*</td>
<td>52.9 (5.3)</td>
<td>51.0 (6.0)*</td>
</tr>
<tr>
<td>L3 (average)</td>
<td>50.7 (2.2)*</td>
<td>49.7 (3.1)*</td>
<td>53.0 (6.7)</td>
<td>50.8 (7.2)*</td>
</tr>
<tr>
<td>L4 (average)</td>
<td>49.9 (2.2)*</td>
<td>49.9 (2.8)</td>
<td>50.4 (6.5)</td>
<td>49.7 (6.7)</td>
</tr>
</tbody>
</table>

*P < 0.05, †P < 0.01 and ‡P < 0.001.
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Abbreviations: RN, retroperitoneoscopic nephrectomy; RAN, retroperitoneoscopy-assisted nephroureterectomy; IAC, intra-abdominal content.
Evaluation of a synchronous twin-pulse technique for shock wave lithotripsy: the first prospective clinical study

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Accepted for publication 27 July 2004

OBJECTIVE
To present the results of the first clinical study of a synchronous twin-pulse technique for extracorporeal shock-wave lithotripsy (ESWL), which is effective for in vitro stone fragmentation and safe when assessed in vivo on animal tissue.

PATIENTS AND METHODS
Fifty patients with urinary stones (35 men and 15 women) were enrolled and treated with the TWINHEADS lithotripter. The entry criteria were: age ≥ 18 years, with a radio-opaque single stone in the kidney or upper ureter, a normal laboratory profile (serum creatinine, liver function, blood, bleeding and clotting times, and prothrombin concentration). The exclusion criteria included lower ureteric stones, patients with urinary tract infection, obstructed urinary tract distal to the stones, or congenital abnormalities. All patients received one session and were evaluated by ultrasonography (US), urinary tract plain X-ray, and complete laboratory investigations before and immediately after treatment, and after 2, 14 and 30 days. Patients requiring retreatment at the 14-day visit received a second session and were re-evaluated after 7 and 14 days.

RESULTS
The mean (SD, range) stone size (longest diameter) was 12.3 (2.6, 9–18) mm. Intravenous sedation was used in 30 patients. There was mild haematuria in 25 patients on the day of treatment. During the follow-up there was no evidence of haematoma, gross renal injury, upper urinary tract obstruction or significant changes in the laboratory investigations. After 14 days, 17 patients (34%) were free of stones, with residual stones of ≤ 5 mm in 20 (40%); they were free of stones at the 1-month follow-up. Thirteen patients (26%) had residual stones of 6–9 mm, but the stones were half or less of the original size. Patients with residual stones of > 5 mm had another ESWL session and were free of stones within 14 days. Thus all patients were rendered stone-free within 1 month.

CONCLUSIONS
Synchronous twin-pulse ESWL is promising, seems safe and effective for treating patients with renal and upper ureteric lithiasis.

KEYWORDS
twin-pulse lithotripsy, urinary calculi, assessment, clinical study

INTRODUCTION
After the marked success of the initial lithotripters for ESWL, several second- and third-generation devices have been developed, using different energy sources, focusing devices and coupling media [1–5], aiming to reduce ESWL-induced renal trauma and pain and thus allow anaesthesia-free ESWL (by reducing the focal zone size and broadening the shock-wave aperture), and to increase the focal peak pressure to improve stone disintegration. However, the tissue effects of newer lithotripters may be equivalent or even greater than those of the earlier models [6]. Also, stone fragmentation is no better, so higher re-treatment rates are reported as a result of the difficulty in keeping the stone in the smaller focal zone [7]. The physics of effective shock waves are the same in all currently available lithotripters. Repeated unidirectional shock waves focused on the stone eventually reduce it to small fragments. In general, shock waves could be applied along all three perpendicular directions in the stone.

On 1999 we developed the bidirectional synchronous twin-pulse technique with variable angles between the shock wave reflectors, and found that it improved the quality and rate of stone disintegration in vitro (especially with a right angle between the reflectors) [8]. The disintegrative efficacy for both artificial and human stones was improved as the number of shock waves and the power were increased [9, 10]. Bidirectional synchronous 90° twin-pulse-induced tissue damage (acutely) appeared to be minimal when compared with a single pulse [11]. On the basis of these studies the first human model, the TWINHEADS 101 lithotripter, was built (FMD, Virginia, USA) and installed in our centre in November 2002. Herein, we report the results of the first prospective clinical study of the safety and effectiveness of bidirectional synchronous twin-pulse ESWL for treating patients with urinary stones.

PATIENTS AND METHODS
The lithotripter comprises two identical electrohydraulic shock-wave generators with dependently adjusted power settings from 7 to 14 kV, and 20–110 MPa at the second focal point (F2), with the peak pressure not significantly different from that of a single shock wave when measured by needle hydrophone (Fig. 1). The device comprises two confocal identical under- and over-table reflectors to permit synchronous shock-waves emission from two perpendicular directions to the same F2. Each reflector has a focal depth of 12.7 cm (distance between the rim of the reflector and F2), and 16 × 30 mm cigar-shaped focal zone. The twin synchronous shock waves are counted as one shock wave. The lithotripter uses X-ray fluoroscopy to locate the stone.

The local ethics committee approved the study protocol; 50 adult patients were enrolled after signing an informed consent.
Inclusion criteria were: patients with a radio-opaque single stone of 5–20 mm in the kidney or upper ureter that had not been treated previously by any means, and a normal laboratory profile (serum creatinine, liver function, blood analysis and coagulation profile). Exclusion criteria included lower ureteric stones, UTI, obstructed urinary tract distal to the stones, congenital anomalies, or coagulation abnormalities.

The evaluation before treatment included a complete physical examination, plain abdominal X-ray, IVU and ultrasonography to assess kidney and ureteric anatomy, laboratory tests including the previous laboratory profile, urine analysis, urine culture, blood urea nitrogen, amylase, and lactate dehydrogenase (using the Synchron LX 20 Pro Autoanalyser, Beckman, USA) for creatinine and the last four tests.

All patients were treated while supine; the heads were coupled using ‘ultrasound jelly’ between the patient and water cushions of the reflectors, these being adjusted to fit the body contour by inflation or deflation (Fig. 2).

No auxiliary procedures were used before ESWL in any patient.

Patients were re-evaluated immediately after the first session with the same schedule as before ESWL (excluding IVU) and again after 2, 14 and 30 days. Patients who required re-treatment after 14 days had a second session using the same schedule and were re-evaluated after 7 and 14 days. Success was defined as no residual stones, as documented by spiral CT when the plain film and ultrasonography did not detect residual fragments. The reporting radiologist was unaware of the patients’ treatment.

The laboratory results and blood pressure before during and after treatments were compared statistically using ANOVA, and when it was significant, with pair-wise comparisons using the initial results as a control for comparison with each follow-up.

RESULTS

Table 1 shows the characteristics of the patients and stones; 41 (82%) patients had stones of >10 mm (five had stones of 17–18 mm), 31 had renal stones (two upper calyceal, four middle calyceal, eight lower calyceal, and 10 had ureteric stones.

All treatments were completed satisfactorily; intravenous meperidine HCl (100 µg/kg) was used in 30 patients (60%) to alleviate discomfort, while 20 (40%) received no anaesthesia. In the first session each patient received 2000 twin shock waves at 60/min with one-step increments in power every 100 shock waves, from 7 to 11 kV. All patients passed ‘gravel’ within 24 h after treatment.

After 14 days, 17 patients (34%) were stone-free, including all those with ureteric stones (three were stone-free after 2 days). There were residual stones of 3, 4 and 5 mm in 5, 10 and five patients with kidney stones (40%), respectively; they were stone-free at the 1-month follow-up. Thirteen (26%) patients with kidney stones had residual stones of 6–9 mm, and half or less of their initial size, and had another session of ESWL; 10 were free of stones after 7 days and three after 14 days. Thus, the stone-free rate was 74% after one session and 100% after two within a month of ESWL.

The overall re-treatment rate was 26% (two sessions only). All patients with upper ureteric stones (regardless of size) and those with renal stones of <10 mm were free of stones after one session, while 13 of 31 (42%) patients with renal stones of >10 mm required a second session (Table 2).

There was mild gross haematuria in 25 patients on the day of treatment, which resolved the next day. Microscopic haematuria was detected in 45 patients immediately after treatment, in 25 at 2 days and in five after 14 days. Mild discomfort was reported in 20 patients during the passage of fragments (those with 3 and 4 mm residual stones and one with 5 mm residual stones), while there was typical renal colic in four patients with 5 mm residual stones.
TABLE 2 The re-treatment rate in relation to stone site and size

<table>
<thead>
<tr>
<th>Site and size, mm</th>
<th>Overall</th>
<th>Kidney</th>
<th>Upper calyx</th>
<th>Middle calyx</th>
<th>Lower calyx</th>
<th>Renal pelvis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>13/37 (35)</td>
<td>0/6</td>
<td>13/31 (41)</td>
<td>0/2</td>
<td>0/1</td>
<td>2/4</td>
</tr>
<tr>
<td>Kidney</td>
<td>0/3</td>
<td>10 mm</td>
<td>1/10</td>
<td>2/4</td>
<td>0/3</td>
<td>2/4</td>
</tr>
<tr>
<td></td>
<td>3/8</td>
<td>50 mm</td>
<td>0/5</td>
<td>1/17</td>
<td>0/3</td>
<td>0/10</td>
</tr>
</tbody>
</table>

SYNCHRONOUS TWIN-PULSE ESWL

auxiliary procedures were required after ESWL in any patient. There was no perirenal or subcapsular haematoma, gross renal injury, or upper urinary tract obstruction detected by ultrasonography or CT at any time.

All laboratory results were within the normal range and there were no significant differences before and after treatment, except in urinary red blood cell counts and total protein. Before ESWL the mean (50) count and protein level was 23.25 (25)/high-power field and 26.25 (40) mg/L, respectively, increasing to 86.8 (27) and 136 (128) immediately after ESWL, and then to 23.6 (34) and 10 (24), respectively (P = 0.001) after 14 days. There were no significant changes in the diastolic (P = 0.54) or systolic (P = 0.45) blood pressure at any time.

X-ray diffraction analysis of the retrieved fragments showed that all stones were calcium-based. Twenty stones were ≥90% calcium oxalate monohydrate (COM), 25 were mixed COM and calcium oxalate dihydrate, and five were ≥90% calcium phosphate dihydrate (brushite).

DISCUSSION

Several mechanisms for stone comminution have been identified. Direct shock-wave mechanisms, attributed to the positive-pressure component, include spallation [1], dynamic fatigue [12] and squeezing [13]. The cavitation bubbles collapse near the stone surface, leading to the formation of high-speed liquid microjets that hit the stone surface and cause fragmentation [14]. The direct stress waves and cavitation work synergistically, rather than independently, to produce effective and successful disintegration of calculi during ESWL [15]. Only a small portion of the collapsing energy (from near the stone) contributes to stone fragmentation, while the remaining larger portion is absorbed by the adjacent tissues, leading to renal injury [16,17].

The optimum use of the stress waves and cavitation in ESWL may help to improve the efficiency of treatment and reduce adverse tissue injury. Several methods to modify the cavitation field were proposed to achieve these targets. Controlled, forced collapse of cavitation bubbles was studied using microsecond tandem shock-wave pulses [18]. A pressure-release reflector was built to reverse the order of positive and negative components of the waveform while maintaining the same peak pressure [19]. A bifocal reflector [20] and a combined electrohydraulic/piezoelectric annular array lithotripter [21] were built to increase the efficiency of stone comminution. A dual-pulse lithotripter with two confocal and opposing reflectors was devised to generate a localized and intensified cavitation field [22]. These techniques generate asynchronous or synchronous pulses in the same axis, either in the same direction or from opposing directions. However, these modifications require confirmation of their clinical feasibility and safety.

The bidirectional synchronous twin-pulse technique generates shock waves simultaneously from two separate reflectors through two axes in non-opposing directions to the same F2. This technique intensifies and localizes the cavitation effects by the interacting focal zones of both reflectors, resulting in a better quality and rate of stone disintegration, especially with a right angle between the axes of the reflectors [8,9]. This device had good in vitro disintegrative efficacy for both artificial (Bon(n)-stones, and plaster of Paris) and human stones (COM, brushite and cystine) with better efficacy as the number of shock waves and the power were increased [10].

In a study of acute tissue effects of the present technique on porcine kidneys, there were neither gross lesions of the surrounding organs, nor subcapsular haemorrhage, or gross parenchymal damage at the outer surfaces of 24, and minimal haemorrhage in coronal sections of four of the kidneys treated by ESWL. Using a single pulse five of six kidneys had large subcapsular haematomas at both the anterior and posterior surfaces, and on coronal sections extending into the parenchyma. This was the case not only for the same count and rate of shock waves, but even when a higher count or rate of twin shock waves were applied [11].

The current study is the first clinical assessment using the bidirectional synchronous twin-pulse technique. All patients with upper ureteric stones were stone-free within 2 weeks of the initial ESWL and those with renal stones were stone-free within 1 month. The rapid clearance of stones could be a result of the fine fragmentation of stones, as most of the retrieved fragments were of < 2 mm and passed easily. Complete stone clearance is uncommon after ESWL, even for matched stone sizes treated with any lithotripter and over a longer follow-up [2,3,6,23,24]. In the present study the complete clearance might be a result of selecting ideal patients, especially with the improved disintegrative efficacy of the new technique. The stone-free rate might be lower with stones > 20 mm or in patients with different selection criteria, and this requires further study.

No re-treatment was required in any patient with upper ureteric stones regardless of size, or for any with renal stones of < 10 mm regardless of location. The clearance rate was better than any previously reported for matched stone size [2,5,24]. Only 13 patients with renal stones (35%) of > 10 mm required a second session. Lingeman et al. [3] reported a 7% re-treatment rate for patients with renal stones of < 20 mm using the HM3 lithotripter in 284 patients evaluable at 3 months, but with no stratification for stone size and with more than two sessions. Bierkens et al. [5] reported the re-treatment rate as the number of treatments divided by the number of patients for five second-generation lithotripters; the rate was 1–1.3% for renal stones (regardless of size) while in the present study it was 1 for stones of < 10 mm and 1.3 for stones > 10 mm. Lalak et al. [25] reported a rate of two sessions/patient for renal stones
of 10–20 mm treated with a Dornier compact lithotripter, and Matin et al. [26] a re-treatment rate of 40% and 10% for patients with renal stones treated with the Dornier MFL 5000 and Modulith SLX lithotripters, respectively, but with no stratification for stone size.

Only four of the present patients (8%) had typical renal colic while passing gravel, compared with up to 43% reported previously [3,27]. Also, there was no obstruction after ESWL in the present patients, compared with up to 17% for different models of lithotripter [5,24,25], but larger stones than that in the present patients, compared with up to 10–16% [2,27]. Also, there was no obstruction after ESWL in any of the present patients, compared with [3,27].


ACKNOWLEDGEMENTS

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CONFLICT OF INTEREST

None declared.

REFERENCES


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Abbreviations: COM, calcium oxalate monohydrate.
Stone-bearing live-donor kidneys for transplantation

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OBJECTIVE

To evaluate potential donor kidneys with asymptomatic calculi detected during screening, and the management of the calculus before, during and after transplantation, as with fewer live donors, marginal kidneys and donors are a significant subgroup in renal transplantation.

PATIENTS AND METHODS

Five live-related donors, with one incidentally detected calculus during their routine evaluation, were accepted for transplantation. Of these, three were detected only on spiral computed angiography. There was no biochemical evidence of a metabolic abnormality or history of stone disease. One donor had elective lithotripsy and another nephrolithotomy under ultrasonographic control immediately after perfusion. The others were transplanted with the calculus in situ. Ureteric reimplantation was by the Leadbetter-Politano technique over a JJ stent.

RESULTS

One recipient patient passed the calculus within 4 h of stent removal. The follow-up ultrasonogram at 3 months showed a stone in only one recipient. In the others, the calculus could not be seen after stent removal. The maximum follow-up was 2 years and graft function has remained normal in all.

CONCLUSIONS

Voluntary kidney donors with one calculus incidentally detected on routine evaluation form a unique group and can be accepted for transplantation in selected cases. Careful follow-up of the donor and recipient is essential, with early intervention if necessary.

KEYWORDS
renal transplantation, donor kidney, urinary calculus, lithotripsy

INTRODUCTION

The live-related kidney transplant programme in the developing world must manage with a relatively fixed donor pool. As there are no national organ-sharing programmes for cadaver transplants in most developing countries, there is a constant shortage of donors, with the inevitable use of marginal donors and kidneys. In the last 30 years 2250 live-related kidneys have been transplanted at our institution but stone-bearing kidneys have never been accepted for transplantation. The possibility of recurrence of stone in the donor’s solitary kidney and the morbidity of stone in the allograft kidney were possibly the main deterrents. This is despite that over the last several years the treatment of stone disease has become easier with ESWL and other endoscopic techniques. A new dimension has been further added to this issue as spiral CT angiography for donor evaluation tend to detect small asymptomatic unobstructive calculi. Therefore, a donor suitable in every other way may be rejected in most transplant programmes in the light of this finding. The same donor may have been accepted earlier, as a conventional angiogram with ultrasonography (US) and/or IVU may not have detected the calculus. In the present series we examined a group of voluntary kidney donors incidentally detected to have one stone during their evaluation. The stone-bearing kidneys were either treated before nephrectomy, at the time of transplantation, or transplanted with the stone in situ, with a view to later intervention, if and when necessary.

PATIENTS AND METHODS

During a 2-year period (2002–2003) five stone-bearing live-donor kidneys were considered for transplantation. All stones were asymptomatic, incidental and confirmed to be single on spiral CT. There was no history of stone disease and the biochemical evaluation included an estimation of serum and 24-h urine calcium, phosphorous and uric acid. All but one donor was aged >45 years. The possibility of further stone formation in the remaining kidney and its morbidity was discussed in detail with the potential donors, and the presence of stone in the allograft kidney and the implications were explained to the potential recipient. The need for regular follow-up was stressed and access to the nearest centre that could offer help in case of a stone-related emergency was ascertained. Informed consent was obtained from all and open-donor nephrectomy carried out with excision of the 11th rib. In one case (Fig. 1a,b) lithotripsy was used, with the passage of fragments after 3000 shocks. The kidney was transplanted 6 weeks later with a residual fragment of 4 mm, confirmed on spiral CT (Fig. 2). An isotope scan was also taken before transplantation in this case. In another (Fig. 3), the kidney was rendered stone-free during surgery with a nephrotomy under US guidance after perfusion. The remaining three kidneys with a solitary calculus of <4 mm were not treated, and were transplanted with the calculus in situ. The vesico-ureteric anastomosis was made using the Leadbetter-Politano technique over a JJ stent. The stents were removed at 6 weeks. Imaging after surgery included a plain X-ray and US. As is the protocol in our transplant programme, all the recipients stayed near the hospital for 6 months, with regular review in the transplant clinic. Imaging was repeated 6-monthly over a follow-up for 2 years, and yearly thereafter.

RESULTS

The period during and after surgery was uneventful in all recipients, and the stents were removed at 6 weeks. One patient passed the stone within 4 h after removing the stent.
The follow-up plain film was negative and the US (Fig. 4) revealed a 4-mm fragment only in the allograft kidney treated by lithotripsy. This was subsequently passed uneventfully. The follow-up was 1–2 years, with the graft function remaining stable in all, with no untoward events or recurrence of stone (Table 1).

DISCUSSION

Stone-bearing kidneys in the live-donor setting have traditionally not been accepted for transplantation in most centres. In our transplant programme, until the first case described here, such potential donors were categorically rejected. The threat of stone recurrence in the single kidney of the donor being the main reason, with the other possible reason being the lack of noninvasive therapy before ESWL. Both the donors described here with the larger calculi that needed treatment before surgery would never have been considered as donors using our usual protocol. However, they were the only suitable related donors and the prospect of obtaining a cadaver kidney for either recipient were remote. Although we accepted a young donor in their third decade initially, we subsequently confined our selection to those with: (a) incidentally detected calculus, confirmed to be solitary on spiral CT; (ii) no history of stone disease or symptoms of stone colic; (iii) a normal metabolic evaluation; (iv) a calculus of <1 cm; (v) age > 45 years; and (vi) able to access local care in case of anuria.

The long-term follow-up of patients with a single episode of stone has shown that the recurrence rate is 10% at 5 years and 22% at 10 years [1]. There are no real differences between patients with and with no recurrence in relation to gender, family history, age at onset or metabolic abnormality [1]. Theories of stone formation suggest that when certain physicochemical conditions are present in the urinary system, stone disease will occur [2]. Urinary stasis, infection, metabolic acidosis, pH changes, supersaturated urine, decreased inhibitor activity and concentrations of minerals like calcium are present at a higher rate in allograft kidneys [3]. Immunosuppression with cyclosporin A is known to produce hyperuricosuria in 50–60% of patients [4], but the incidence of uric acid stones is only 0.2% [3]. Although a multifactorial cause has been suggested for transplant stones, the risk of forming calcium-containing stone was associated with greater water excretion and more concentrated and alkaline urine [5]. Despite these risk factors, the incidence of stone in transplant kidneys continues to be very low, at 0.2–1.7% [3,6]. In the present series, the initial radiological screening by US detected only two of five calculi. The others were detected only on spiral CT angiography, routinely used for donor evaluation at our centre after the final selection is complete. Spiral CT is extremely sensitive and can detect very small stones and even calcifications or Randall’s plaques [7] that may not be clinically significant. It is quite likely that with spiral CT angiography replacing conventional angiography, more such calculi would be detected, creating a dilemma both in the indication and method of management [8].

The calculus could be treated before or after transplantation. The advent of ESWL has made the treatment of small stones easier. If lithotripsy is used before donor nephrectomy the surgeon could either wait until all the fragments are cleared, or proceed with transplantation even in the presence of small fragments. Long-term results of ESWL on renal function in patients with a solitary kidney has shown that there is no statistical evidence of a deterioration in renal function [9]. In the present series the kidney treated with ESWL before surgery showed no obvious abnormality, either on isotope scan or at

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**FIG. 1.** A plain X-ray (a) and IVU (b) showing the right upper pole calculus.

**FIG. 2.** Spiral CT showing the residual calculus after lithotripsy.

**FIG. 3.** CT angiogram, showing the lower pole calculus.

**FIG. 4.** Follow-up ultrasonogram showing a residual calculus in the recipient kidney.
nephrectomy 6 weeks after lithotripsy. On exploring a kidney soon after ESWL there might be oedema or tissue friability that cannot be assessed accurately by routine clinical testing. What is not known is the ideal waiting period after lithotripsy. During surgery the stone could become dislodged during manipulation of the donor kidney or at any time during the procedure. Stones in cadaver kidneys detected before transplantation have been removed during surgery using a flexible cystoscope introduced through a pyelotomy after US screening [3]. They have also been removed during surgery in a series of live donors, using a 6.9 F rigid ureteroscope passed through the ureteric stump, using a combination of the holmium laser and basketing [8]. In one case in the present series, we opted for nephrotomy and removed the 1.5 cm calculus at the time of nephrectomy.

Asymptomatic donor renal calculi of <4 mm can be managed conservatively and often there is spontaneous passage in the recipient [3]. However, the compliance has to be very good to follow this option, and the patient counselled accordingly. If the stone is 5–15 mm, successful treatment of the allograft with lithotripsy is possible with the patient prone [10]. The allograft kidney is denervated and classic colic may not be a presentation. Therefore, close monitoring is essential, as the altered pain response makes managing steinstrasse difficult. As these patients are more prone to infection in their immunosuppressed state, they may develop recurrent UTI. Decreased urine output, rising creatinine, anuria, hydrenephrosis on US, or signs and symptoms of rejection, are the other modes of presentation. Undetected hydrenephrosis can cause progressive deterioration of renal function. If associated with infection, in an immunocompromised state this can even be fatal [11]. An emergency nephrostomy may be needed in such a situation [8].

The management of allograft ureteric calculi is particularly challenging. As the ureteroneocystotomy may be at the dome, anterior wall or high on the posterior wall, engaging the ureteric orifice for ureteroscopy may be difficult and often unsuccessful [3]. In the Politano-Leadbetter type of vesico-ureteric anastomosis, the position of the neo-orifice offers better access to the ureter for ureteroscopy, and a firm base for balloon dilatation, if needed. It is also important to keep the ureter of the right length to facilitate endoscopic manipulation. Even so, the lack of soft-tissue support makes rigid ureteroscopy very risky. One way to counter this problem is to use a ‘superstiff’ Amplatz guidewire after access has been made [12].

This offers support to the allograft ureter in the way that retroperitoneal structures support the native ureter. Percutaneous nephrolithotomy in the allograft is reserved for the larger calculus and may need US screening [10]. With the change in axis and position of the kidney, three-dimensional visualization with US may give a better orientation than fluoroscopy.

The present follow-up was relatively short, with no untoward events or recurrence of stone. In a series of 10 patients with a longer follow up of 33 months in the recipients and 36 months in the donors, no new stones had formed [8].

In conclusion, asymptomatic calculus-bearing voluntary donor kidneys detected during screening can be considered for transplantation in carefully selected and compliant cases. The calculus can be managed conservatively, treated with lithotripsy or managed during surgery, depending on the size. Ureteric reimplantation should be such that it facilitates ureteroscopy later, if required. A high index of suspicion should be maintained and early intervention planned to avoid complications. A long-term vigilant follow-up for both donor and recipient is essential to accurately determine the outcome.

**CONFLICT OF INTEREST**

None declared.

### TABLE 1 The characteristics of the stones, and the evaluations for kidney function after transplantation in the five donors

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial stone size, mm</td>
<td>12</td>
<td>15</td>
<td>4</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Treatment for stone</td>
<td>ESWL</td>
<td>Nephrolithotomy</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>Stone size after surgery</td>
<td>4 residue</td>
<td>Nil</td>
<td>4</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Nadir creatinine, mg/L</td>
<td>15</td>
<td>15</td>
<td>12</td>
<td>16</td>
<td>11</td>
</tr>
<tr>
<td>Stone on imaging after surgery:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>plain film</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>US</td>
<td>4 mm</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>Documented stone passage?</td>
<td>Yes</td>
<td>–</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

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Abbreviations: US, ultrasonography.
Managing varicoceles in children: results with microsurgical varicocelectomy

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OBJECTIVE

To report our experience of microsurgical subinguinal varicocelectomy in boys aged ≤18 years.

PATIENTS AND METHODS

Boys aged ≤18 years treated with microsurgical varicocelectomy between 1996 and 2000 at one institution were retrospectively reviewed. Indications for surgery included ipsilateral testicular atrophy, large varicocele or pain. Microsurgery was assisted by an operating microscope (×10–25) allowing preservation of the lymphatics, and the testicular and cremasteric arteries. Patient age, varicocele grade, complications and follow-up interval were recorded.

RESULTS

In all there were 97 microsurgical subinguinal varicocelectomies (23 bilateral) in 74 boys (mean age 14.7 years). Left-sided varicoceles were significantly larger (mean grade 2.9) than right-sided (mean grade 1.4) varicoceles. The mean follow-up was 9.6 months. There were four complications: two hydroceles, of which one resolved spontaneously after 4 months; one patient had persistent orchialgia that resolved after 8 months; and one developed hypertrophic scarring at the inguinal incision site. There were no infections, haematomas or intraoperative injuries to the vas deferens or testicular arteries. All boys were discharged home on the day of surgery.

CONCLUSIONS

Microsurgical subinguinal varicocelectomy in boys is a safe, minimally invasive and effective means of treating varicoceles. Compared with published results of the retroperitoneal mass ligation technique, which has a 15% overall complication rate and a 7–9% hydrocele occurrence rate, the microsurgical subinguinal approach appears to offer less morbidity, with a 1% hydrocele rate. We consider that microsurgical subinguinal varicocelectomy offers the best results with lower morbidity than other techniques.

KEYWORD

varicocele, paediatric, microsurgery, outcomes

INTRODUCTION

Managing varicoceles in boys remains controversial. Of adolescents with varicoceles,
95% have at least a left-sided varicocele and 22% are bilateral [1]. Varicoceles are relatively uncommon in prepubertal boys and increase in incidence from the age of 10–15 years, up to 13.7–16.2% [2]. Previously, most varicoceles in boys were not treated, because the detrimental effects on future fertility and testicular function were not recognized [3–6]. Several studies then reported that early correction of varicoceles could prevent the decline in fertility found among men with varicoceles discovered in adolescence [3,5,7,8]. Absolute indications for varicocelectomy in children include: testicular size discrepancy of >2 mL on ultrasonography, a >2 SD decrease in testicular size compared with normal growth curves, and varicocele-related pain (orchialgia) [9,10]. However, operating on even large or bilateral varicoceles in adolescents with normal-sized testes remains controversial.

Once the decision has been made to correct an adolescent varicocele the method to be used becomes an important consideration. The best repair technique to correct paediatric or adolescent varicocele is still debated. Recurrence rates are higher in adolescents after repair, at 9–16% [11]. These high failure rates are a result of the technical difficulties in ligating the very small peri-arterial veins or unrecognized communicating internal spermatic veins, cremasteric, deferential, gubernacular, suprapubic and retroperitoneal veins [9,11,12]. Various surgical approaches exist for this procedure, including retroperitoneal, high inguinal, subinguinal, laparoscopic, and percutaneous venous sclerotherapy. The aim of any repair is an effective, durable cure with a minimum risk of complications. The most frequent complications associated with varicocelectomy repair include hydroceles, testicular atrophy and recurrence.

We report our experience using the microsurgical subinguinal varicocelectomy (MSV) in 74 boys; we consider that the enhanced visualization provided by the operating microscope allows a more thorough dissection of the small testicular vessels and lymphatics, resulting in a durable cure with a minimum risk of complications.

PATIENTS AND METHODS

All boys aged ≤18 years treated with MSV at the New York–Presbyterian Hospital Weill–Cornell Medical Center between 1996 and 2000 were included in this analysis; in all, 74 boys were identified, all diagnosed with a varicocele by physical examination. Boys with impalpable varicoceles were excluded from the analysis. Surgical indications included the presence of a clinically palpable varicocele and testicular asymmetry in the absence of other clinical symptoms, or palpable varicocele with ipsilateral orchialgia with no other identifiable causes.

The MSV technique used in this series was well described previously [13,14]. Briefly, patients were placed supine and under general anaesthesia. The external inguinal ring is palpated and marked. A 2.5–3 cm incision is made in the skin above the external inguinal ring (Fig. 1a). Dissection is carried down until the spermatic cord is identified and mobilized (Fig. 1b). We deliver the testicle and examine the gubernaculum to identify any varicose veins between the gubernaculum and the testis. Any large veins are clipped and divided (Fig. 1c). The testis is returned to the scrotum and the cord layers are clipped and divided (Fig. 1d). The testis is then palpated and examined for the presence of varicoceles, with a median clinical grade of 3 (Fig. 1e). The testis is then delivered to the scrotum and the cord layers are clipped and divided (Fig. 1f). The testis is then palpated and examined for the presence of varicoceles, with a median clinical grade of 3 (Fig. 1g).

RESULTS

In all, the 74 boys (mean age 14.7 years) underwent 97 MSVs; 23 boys had bilateral palpable varicoceles and 51 had unilateral varicoceles, with a median clinical grade of 3 on the left and 1 on the right. The mean operative duration was 66 min for unilateral and 112 min for bilateral MSVs. At least one testicular artery was identified and preserved in all cases. There were no injuries to the vas deferens and all patients were discharged home on the day of surgery.

The mean follow-up was 10.1 months, during which there were four (5%) complications: two boys (2%) developed hydroceles, one of which resolved spontaneously after...
4 months; one boy (1%) reported orchialgia that resolved after 8 months; and one boy reported hypertrophic scarring. The indication for varicocelectomy in the boy with orchialgia was pain. There was no orchitis, infection or haematoma, no recurrent varicoceles during the follow-up, and no patient had progressive testicular atrophy or hypotrophy. No patient complained of prolonged orchialgia.

**DISCUSSION**

The treatment of adolescent varicoceles in cases of testicular atrophy and orchialgia is firmly established [3,5,7,8]; what is less clear is the best way to correct varicoceles in children. There are several surgical approaches to repair varicoceles and percutaneous sclerotherapy is still used. When comparing repair techniques, the best approach is that providing the highest success rate with the lowest rate of complications and morbidity.

Results of the surgical techniques of varicoceole repair vary widely. Percutaneous sclerotherapy has a low risk of testicular atrophy but has reported recurrence rates of 9–26% for the retrograde and 2.9–7.1% for the antegrade approach, and a rate of hydrocele formation approaching 14% [11,15–17]. Inguinal varicocelectomy without microsurgical aid has a reported recurrence rate of 15–16%, with a 10% postoperative hydrocele formation rate, secondary to inadvertent ligation of testicular lymphatics [11,15]. Retroperitoneal ligation of varicose veins with preservation of the testicular artery (the modified Palomo procedure) has a reported recurrence rate of 2.5–13.6%, with at least a 10% risk of postoperative hydrocele formation [15,18]. Laparoscopy has been used for various surgical approaches in urology, and the repair of the adolescent varicocele is no exception. The main advantage of laparoscopy is that it is minimally invasive, as well as using superior optics and magnification of the laparoscopic camera. However, the recurrence rate with this procedure with preservation of the testicular artery has been reported to be 2.2–25%, with a 12.5% risk of postoperative hydrocele formation [11,19,20].

Previous reports of MSV in boys found no recurrence, no persistent postoperative hydroceles and no cases of testicular atrophy [21,22]. In the present series of 74 consecutive boys treated by MSV, most had large unilateral varicoceles, and there were no recurrences on follow-up. The immediate complication rate was 5% (four of 97), with two hydroceles after surgery, one of which resolved spontaneously after 4 months, giving a 1% risk of hydrocele formation. There were no cases of ischemic orchialgia or testicular atrophy among the present patients.

We think that using the operating microscope enables a better dissection around the testicular artery and allows for better preservation of the testicular lymphatics, thus decreasing the risk of injury and postoperative hydrocele formation. This procedure causes minimal postoperative morbidity, with incision sizes comparable to those used to place laparoscopic trocars. The high success rate and the low risk of morbidity and complications make MSV the procedure of choice to repair varicoceles in adolescent boys.

**CONFLICT OF INTEREST**

None declared.

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Abbreviations: MSV, microsurgical subinguinal varicocelectomy.
Perineal anastomotic urethroplasty for managing post-traumatic urethral strictures in children: the long-term outcome

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OBJECTIVE
To evaluate the long-term results of one-stage perineal anastomotic urethroplasty for post-traumatic paediatric urethral strictures.

PATIENTS AND METHODS
Thirty-five boys who had a perineal anastomotic urethroplasty for post-traumatic bulbous or posterior urethral strictures between 1991 and 2003 were analysed retrospectively. Patients were followed up for a mean (range) of 46 (6–132) months by a history, urinary flow rate estimate, retrograde urethrography and voiding cysto-urethrography.

RESULTS
The mean (range) age of the patients was 11.9 (6–18) years. The estimated radiographic stricture length before surgery was 2.6 (1–5) cm. The perineal anastomotic repair was successful in 31 of 35 (89%) patients. All treatment failures were at the anastomosis and were within the first year. Failed repairs were successfully managed endoscopically in two patients and by repeat perineal anastomotic repair in the remaining two, giving a final success rate of 100%. All boys are continent except two who had early stress incontinence, and that resolved with time. There was no chordee, penile shortening or urethral diverticula during the follow-up.

CONCLUSIONS
The overall success of a one-stage perineal anastomotic repair of post-traumatic urethral strictures in boys is excellent, with minimal morbidity. Substitution urethroplasty or abdomino-perineal repair should be reserved for the occasional patients with concomitant anterior urethral stricture disease or a complex posterior urethral stricture, respectively.

KEYWORDS
urethra, urethral stricture, pelvis, perineum

INTRODUCTION
Urethral stricture disease in children most commonly results from pelvic fracture, straddle injuries or urethral manipulation [1]. Several groups have recommended endoscopic urethrotomy or urethral dilatation as effective first-line therapy [2–6]. However, reported results are conflicting and many procedures are often required to achieve success [3,5].

Most principles applicable to the open repair of post-traumatic urethral injuries in children are the same as in adults. However, children differ in having a more abdominally located bladder and prostate, and less capacious pelvis. Because of these differences it has been claimed that transperineal urethroplasty, successful in adults, is technically more difficult in the confined perineum of a child [9].

Post-traumatic urethral strictures have been reviewed infrequently in children, and most published series of open perineal urethral reconstruction have included few patients [10–13] or lacked a long-term follow-up [6,8]. This induced us to examine the long-term success of transperineal urethral reconstruction in children with post-traumatic stricture, in an attempt to analyse the clinical outcome and complications of such approach.

PATIENTS AND METHODS
The computerized surgical records at our institute were reviewed to identify children (≤18 years old) who had had a transperineal urethroplasty for post-traumatic stricture disease between 1991 and 2003. In all, 35 boys, with a mean (SD, range) age of 11.9 (3.4, 6–18) years were identified. Their hospital and office charts were reviewed, noting patient age, urinary retention at the time of presentation, cause of stricture, treatment complications and the duration of catheter drainage after surgery. In all patients the evaluation before surgery included a history, physical examination, retrograde and voiding cysto-urethrography. Urethroscopy was performed with the patient under anaesthesia, to delineate further the urethral anatomy and characteristics of the stricture.

Intravenous antibiotics were administered peri-operatively and then tailored according to urine sensitivity. All surgical repairs were approached through an inverted Y-shaped perineal incision, with the patient in an exaggerated lithotomy position. The bulbar urethra was dissected down to the proximal end of the strictured segment, which led to the apex of the prostate. After excising all scarred tissue, the distal urethral end was spatulated. After mobilizing the anterior urethra a tension-free mucosa-to-mucosa anastomosis was made with four to six sutures of 5/0 polyglycolic acid over a silicon Foley catheter. Development of the intercrural space and inferior pubectomy, using bone nibbling forceps, were required to achieve a tension-free anastomosis in eight (23%) and six (17%) patients, respectively. The operation was completed by inserting a suprapubic
cystostomy tube and closing the perineal wound with a drain.

Urethral stenting with a silicon catheter and suprapubic cystostomy drainage were maintained for 21–28 days after surgery. After removing the urethral catheter a gravity voiding film, with contrast medium infused through the suprapubic cystostomy tube, was taken to confirm the integrity of the repair, and if satisfactory the suprapubic cystostomy catheter was removed 1 day later.

All patients had a urethral injury associated with trauma, caused by a motor vehicle in 23 (66%), a train in three (9%) and a fall from height in nine (26%); the trauma was associated with a pelvic fracture in 16 (46%) patients. The classical presentation in all patients was with a suprapubic cystostomy tube and scheduled for delayed or repeated correction of a urethral stricture. Seven patients (20%) were referred to us after previous attempts at repair (one to six procedures in each), including repeated endoscopic internal urethrotomy in six, and failed attempts at open reconstruction of posterior urethral distraction defects in seven. The interval between the original trauma and repair in new cases, and since the last repair in recurrent cases, was 3–12 months.

The stricture length and location were analysed by reviewing urethrography and operative details; the mean (range) length was 2.6 (1–5) cm and 24 (69%) patients had strictures affecting the posterior urethra, making it the most common site for stricture formation in the series. The bulbous urethra was the site of stricture in nine patients (26%), with strictures identified in the penile and bulbous urethra in two (6%).

All patients had a one-stage perineal repair; retropubic or transpubic exposure was not required in any case. There were no early complications during the hospital stay after surgery. Gravity cysto-urethrography through the suprapubic cystostomy tube within 28 days of surgery showed widely patent anastomoses with no extravasation in all patients (Figs 1 and 2).

The mean (range) follow-up was 46 (6–132) months. In four patients with posterior urethral disruption strictures the disease recurred and open surgical revision (perineal approach) was required in two, and the remaining two were managed by visual internal urethrotomy. In no other patient was a secondary procedure required. All recurrent strictures were short, at the site of the anastomosis, and within the first year after surgery. Thus, the primary success rate was 89% and the overall success rate 100%. Intermittent catheterization was not needed in any patient to maintain a patent repair.

All patients voided with no symptoms and were continent (except for two who had early stress incontinence, which resolved with time). The quality of erection was not uniformly assessed. There was no chordee, urethral shortening or urethral diverticula during the follow-up.

DISCUSSION

Paediatric urethral stricture disease represents an uncommon but difficult urological problem. Such urethral strictures generally have an acquired cause, as congenital and infectious strictures are rare. There are several treatments to manage urethral strictures in children; in general they include urethral dilatation, endoscopic visual internal urethrotomy and open urethral reconstruction. Dilatation is often used as an initial treatment, with some success [6], but the long-term results have been poor and this procedure should not be considered curative [8].

Endoscopic urethrotomy in children has been described by various groups, with a success rate as high as 86% in selected series [2–7]. In many cases many urethrotomies were needed, which can further complicate open urethral reconstruction when required [2,3]. Poor long-term results for direct-vision internal urethrotomy have been reported [14].

Open reconstruction of urethral strictures in children follows the same principles as that in adults. Historically, a one-stage Badenoch pull-through procedure of the bulbous urethra was used for strictures of <2 cm [15], while longer strictures were managed by transpubic anastomotic urethroplasty [16,17], or by a two-stage substitution urethroplasty and scroto-urethral inlay [18,19]. The abdomino-perineal repair was reserved for complex
posterior urethral defects, which included those associated with bladder neck abnormalities, fistula to the bladder base or rectum, periurethral cavities and those patients with skeletal abnormalities precluding perineal access [20,21]. In the 1970s Turner-Warwick [22] popularized a delayed one-stage perineal approach, comprising urethral mobilization followed by bulboprostatic anastomosis, to bridge defects of up to 2.5 cm. This procedure became the standard repair for short strictures, while substitution urethroplasty or transpubic urethroplasty continued to be used for longer defects or complex posterior urethral defects, respectively. Buccal mucosa has proved to be a successful grafting material, especially as a patch, for long-segment strictures not amenable to anastomotic urethroplasty [23].

Open reconstruction of urethral strictures in children has generally given favourable results, but most published series of open perineal urethral reconstruction in children have included few patients [10–13] or had only a short follow-up [6,8]. The present series included 35 children with post-traumatic urethral strictures, representing the second largest series reported after that of Koraitim [24]. The present primary and overall success rates were 89% and 100%; our results using a single perineal approach may have been skewed by the relatively short mean stricture of 2.6 cm. However, this length may represent the norm in children, as it is comparable to that in other reported series of retropubic or transpubic dissection [7,11]. In addition, the large series of post-traumatic membranous urethral disruptions in children reported by Koraitim [24] had a high success rate using the perineal (93%) and transpubic (91%) approach for bulboprostatic anastomosis. Thus, it appears feasible to approach paediatric stricture repair through a perineal incision, converting to a transpubic approach only if a tension-free anastomosis is not feasible. Inferior pubectomy through the perineal incision was required in 17% of the present patients to achieve a tension-free anastomosis.

Transpubic or retropubic dissection has been advocated to reconstruct paediatric urethral strictures [7,11,24]. In the present series all bulbar urethral strictures and membranous urethral disruptions were reconstructed through a single perineal incision, with no retropubic or transpubic dissection. We do not favour a transpubic approach, and at least in one large series of adult posterior strictures it has not been necessary [25]. The increased morbidity of the transpubic approach was described in adults [26]. Difficulties during stricture repair because of the smaller urethra in children are offset by a shorter stricture and more superficial placement of the urethra in the perineum.

Four patients (11%) in the present series had recurrent stricture after primary perineal urethroplasty, all having a stricture of >4 cm. Andrich et al. [27] reported a similar incidence (14%) of re-stricture 15 years after anastomotic urethroplasty. Previously, managing the failed anastomotic repair included the less than satisfactory staged scrotal inlay procedure, or even urinary diversion in the most severe cases. However, as shown here, most failures were short strictures, at the anastomosis, and responsive to optical urethrotomy (two patients) or repeat perineal anastomotic repair (two). Similarly, others have reported successful endoscopic management of recurrent anastomastic strictures and attribute this success to the short stricture and a decrease in periurethral fibrosis after perineal repair [28].

In conclusion, the reference standard for treating post-traumatic urethral strictures in children is transperineal one-stage bulboprostatic anastomosis. Development of the intercorral space and inferior pubectomy is important in achieving a tension-free anastomosis in patients with long strictures. This procedure should be attempted first in every case and a transpubic procedure used only if a tension-free anastomosis cannot be made through the perineum.

CONFLICT OF INTEREST
None declared.

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Ectopic adrenocortical tissue found at groin exploration in children: incidence in relation to diagnosis, age and sex

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OBJECTIVE
To assess the incidence of ectopic adrenocortical tissue (EACT) in the groin in children, and examine the relationship between the incidence and the underlying diagnosis, age and sex.

PATIENTS AND METHODS
From computer records, all groin explorations between 1988 and 2002 in patients ≤15 years old were identified. Cases of EACT were identified from computer histology records, and the incidence in different groups compared.

RESULTS
Of 935 groin explorations, EACT was identified in 25 (2.7%); there were no cases in girls. The incidence was 0.7% at inguinal herniotomy (IH), 4.1% at ligation of the patent processus vaginalis for communicating hydrocele (P = 0.03 vs IH), and 3.3% at exploration for undescended testes (P = 0.02 vs IH). In boys with undescended testes, the incidence of EACT was similar in different age groups (0–7 years, 3.3%; 8–15 years 3.2%, P = 0.96).

INTRODUCTION
Ectopic adrenal tissue was first identified in the vicinity of the adrenal gland by Morgagni as early as 1740 (cited in [1]). Since then, nodules of ectopic adrenal tissue have been identified at many sites close to the adrenal gland, e.g. the kidney and the coeliac axis [2,3], and in association with the genitalia [4,5]. The appearance is of a small but distinct, soft, round, yellow nodule. In the groin they are found adherent to the spermatic cord or hernial sac, or close to the testis. The golden yellow of the nodule is similar to that of the adrenal gland itself, and nodules are typically 1–4 mm (Fig. 1). Microscopic examination shows distinct layers of cells typical of adrenal cortex (Fig. 2).

Autopsy studies have shown an incidence of >50% for ectopic adrenal tissue near the adrenal gland in neonates and children [6]. Nelson [2] cited an autopsy incidence as high as 90%. In adults the incidence is probably lower, reported as 1% [7] to 32% [3]. In the region of the testis, the incidence is probably 7.5–15% in neonates [8]. Dahl and Bahn [8] report that Wiesel [9] found a much higher incidence in neonates (>70%) but found no ectopic adrenocortical tissue (EACT) among 15 children and adults, all >1 year old. Some doubt has been cast on Wiesel’s findings in neonates [8].

The explanation for the association with the gonad is the close proximity of the developing adrenal cortex to the genital ridge in the embryo [10]. Ectopic adrenal tissue is thought to arise when clusters of cells separate from, or arise outside, the main body of the adrenal cortex, and then adhere to, or become associated with, the gonad or adjacent tissues [1]. The ectopic tissue can then migrate with the gonad to distant sites. The adrenal medulla arises separately by migration of cells from sympathetic ganglia, which go on to invade the adrenal cortex around its central vein [10]. This may explain why ectopic adrenal nodules more distant from the adrenal gland are normally composed only of adrenal cortex [3].

Until recently, the incidence of EACT in the groin was unclear. In the last 20 years several case series have begun to clarify the frequency of EACT as an incidental finding at groin exploration [11–19]. Many of these series suggested a difference in incidence according to underlying diagnosis and sex of the patient, but the case series were small, and statistical analysis was not reported. Despite increasing reports, many surgeons are unaware that EACT can be found in the groin. The senior author of the present paper (R.B.K.) has routinely excised nodules suspected to be EACT, whenever encountered, for >15 years. This provided an ideal opportunity to study the incidence of EACT in more detail than previously possible.

PATIENTS AND METHODS
All operations on children aged <16 years under the care of the senior author (R.B.K.) were identified by a search for operative codes in the operating theatre department database. Only complete years were included, leaving 15 years for analysis (1988–2002 inclusive). Groin explorations were identified according to the operative codes, and classified according to operation performed: inguinal herniotomy (IH); ligation of patent processus vaginalis (LPPV) for communicating hydrocele; or orchidopexy/orchidectomy for undescended testes (UDT). While inguinal hernia and communicating hydrocele share a common aetiology, at operation the findings differ, therefore cases coded as IH and those coded as LPPV for communicating hydrocele...
are treated in this study as distinct underlying diagnoses. Cases with an UDT and a hernial sac were treated as part of the UDT group, as the presence of the hernia was considered to be part of the pathology of the condition. Where records suggested both inguinal hernia and hydrocele/hydrocele of the cord, the cases were excluded.

To identify patients with EACT, the histology results of each patient were checked using the computerized hospital pathology system. The data were also checked by recalculating the incidence using diagnoses from independently entered hospital coding records, by a separate search of the histology database for EACT cases, and by checking the notes of EACT cases to ensure that the operative and diagnostic codes were correct.

The incidence of EACT in different diagnostic groups was compared using the chi-squared test. For a comparison with published reports, data from these were combined to provide values for the incidence of EACT in different diagnostic categories, and for comparing boys and girls. Only English-language studies with comparative data on IH and UDT were included. For a comparison of male vs female IH, studies were included if sufficient detail was given to derive data on the incidence of EACT at IH in both sexes. Groin explorations in girls were assumed to be for IH. Published data did not provide sufficient detail or values to compare LPPV with IH, or to compare age groups. The combined values were analysed using chi-squared tests, as described above.

RESULTS

After exclusions, 862 patients were identified, with 25 cases of EACT; of these, 73 had bilateral operations, giving a total of 935 groins explored, and an overall incidence of 2.7%. The median (range) nodule diameter was 3 (1–7) mm. Using operative coding data, the incidence of EACT among different groups was; IH 0.7%, UDT 3.3% and LPPV 4.1%. There were significant differences in incidence between IH and UDT, and between IH and LPPV (Table 1).

The incidence of EACT according to values derived from diagnostic coding was: IH alone, two of 245 groins (0.8%); UDT, 16 of 451 groins (3.5%); hydrocele alone, seven of 177 groin explorations (4.0%). Again there was a significant difference in the incidence of EACT in IH vs UDT, and in IH vs LPPV (both P = 0.03). Combined values from previously published reports [12,15,16,19] similarly show a significantly higher incidence of EACT in groins explored for UDT than in those explored for IH (6.2% vs 1.7%, P < 0.001).

No cases of EACT were found among 35 groin explorations in girls in the present series. In view of the differences in incidence between different diagnoses (see above), the incidence in girls in published studies [12,15,16,19,20] (presumably all, or almost all, inguinal hernias) was compared to the incidence of inguinal hernia in boys. There was no significant difference in the incidence of EACT between boys and girls with inguinal hernia in these studies: boys, 19 of
The analysis of EACT according to age was confined to the largest diagnostic group, i.e. boys undergoing exploration for UDT, who were divided into two groups. Of 303 boys aged 0–7 years with UDT, EACT was detected in 10 (3.3%); and of 187 boys aged 8–15 years inclusive EACT was detected in six (3.2%). There was no significant difference in the incidence of EACT between the groups ($P = 0.38$).

A computerized search of the histology department database for cases of EACT correctly identified 82% of the cases identified by searching records by hand, and found no additional cases in children. Two further adult males with EACT were identified, aged 16 years (varicocele ligation) and 22 years (orchidectomy for embryonal carcinoma).

**DISCUSSION**

This study presents the largest series of cases of EACT reported to date, and suggests an incidence of around 2% in children at groin exploration. This study is the first to report significant differences in incidence according to the underlying diagnosis. Analysis of combined data from published studies confirms a similar pattern of differences in incidence according to diagnosis.

Several explanations could be offered. The differences found in the present study could be a result of chance, but previous studies consistently show a similar difference between IH and UDT, including a prospective study with the highest reported incidences of EACT for IH (5.2%) and for UDT (10.9%) [13]. There may be some inaccuracy in our operative department coding, but cross-checking of diagnostic codes and patient notes identified no significant coding inaccuracy. The difference in incidence might arise through a more thorough dissection in one operation than another, as suggested previously [15,16]. Although plausible, the degree of dissection in all three operations is similar in our practice, and the vast majority of these operations were performed (or supervised) by one surgeon (R.B.K.).

A more interesting explanation might be that some difference in the mechanism or timing of organ formation or gonadal descent leads to a greater likelihood of nodules of EACT migrating with the gonad in boys who develop UDT than those who develop inguinal hernia alone. Alternatively, involution of EACT may vary between different diagnoses.

It is unclear why the incidence of EACT should differ between cases of inguinal hernia and cases of communicating hydrocele, which share the common underlying aetiology of defects in closure of the processus vaginalis [21]. There may be differences in embryological development that favours migration of EACT in those where the processus remains completely open. However, in the two reports that give any specific details of cases of communicating hydrocele [18,19], no cases of EACT were found amongst 38 operations. One paper may have included congenital hydrocele cases with hernias [12]. In the remainder it is unclear whether hydrocele cases were omitted, or included with IH cases.

Savas et al. [18] noted the young age of the IH cases in which they found EACT, none being >8 months old. If the incidence of EACT is higher in neonates, as suggested [3,4,6,7], the younger age at which IH is often performed might lead to identifying EACT before involution, and consequently exaggerate the incidence in IH patients. In the present series, 29% of IH patients were <1 year old at operation, compared to 2% of UDT patients. The present data do not suggest that there is any significant involution of EACT with increasing age among UDT patients, but few UDT patients were <1 year old.

Only two young adult cases were identified during a 15-year period. In published reports there are many more reported cases of EACT in children than in adults, but no incidence values for adults have been published. A lower incidence in adults could be a result of involution, less complete dissection, differences in underlying diagnosis, or merely that EACT might be harder to identify in the adult groin.

The importance of nodules of EACT in the groin should not be overstated. There have been reported cases of phaeochromocytoma developing in the groin [22], and of Cushings syndrome associated with ectopic adrenal tissue [23], but these are very rare. In agreement with other authors, we consider it reasonable to excise a nodule of EACT found incidentally, but not to risk injuring spermatic cord structures by systematically searching for it. EACT is of interest mainly as an anatomical curiosity, but it appears to vary in incidence between common congenital abnormalities. Elucidating the mechanism behind this variation might shed some new light on the pathophysiology of these conditions.

In summary, EACT was found incidentally in ~3% of groin explorations in children. There is evidence that the incidence varies according to the underlying congenital abnormality leading to surgery. The apparently lower incidence of EACT in girls might reflect differences in underlying diagnosis. There was no evidence of a lower incidence of EACT with increasing age among boys with UDT.

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**CONFLICT OF INTEREST**

None declared.

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Abbreviations: EACT, ectopic adrenocortical tissue; IH, inguinal herniotomy; LPPV, ligation of patent processus vaginalis; UDT, undescended testis.
Cystitis glandularis in children

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OBJECTIVE

To assess the characteristics of cystitis glandularis in children.

PATIENTS AND METHODS

Three cases of cystitis glandularis in children are described, occurring in boys aged 9–13 years. The presenting symptoms were gross haematuria in the first patient and frequency and urgency in the second. The third patient was asymptomatic and the lesion appeared as a wide thickening of the bladder wall on follow-up ultrasonography for previous surgery. In all patients, a polypoid bladder mass was found at cystoscopy and diagnosed at histology. The endoscopic resection, with long-term antibiotic prophylaxis, was the treatment of choice, with no recurrence at 12–30 months of follow-up.

CONCLUSION

Cystitis glandularis has been rarely described in children, and is probably related to chronic or recurrent infections or an inflammatory reaction. Its potential premalignant significance is still the subject of debate.

KEYWORDS

cystitis glandularis, urinary tract infections, paediatric

INTRODUCTION

Cystitis glandularis is a proliferative and metaplastic disorder of the bladder mucosa rarely reported in children; even in adults its incidence and clinical significance are not known exactly. The occurrence of cystitis glandularis is closely related to other proliferative changes of the bladder mucosa, e.g. submucosal masses of epithelial cells ('Brunn's nests'), epithelial crypts and the subepithelial fluid-filled cysts of cystitis cystica. In cystitis glandularis the transitional epithelium undergoes metaplasia into a columnar type, which may or may not secrete mucus. It is frequently found lining the cysts of cystitis cystica, and many authors therefore term it as 'cystitis cystica glandularis' [1–4].

The diagnosis is generally made on histopathological examination. The correlation of cystitis cystica glandularis with the development of bladder tumours, e.g. adenocarcinoma and TCC, is debatable. Only a few cases of cystitis glandularis have been reported in children [5,6] and here we describe three more.

PATIENTS AND METHODS

Patient no. 1 was born with the exstrophy-epispadias complex; he had primary closure of the exstrophic bladder within the first 24 h of life and genital reconstruction at 20 months old. He had partial continence with spontaneous transurethral voiding every 60–90 min, a voided volume of ≈120 mL, no residual urine and recurrent UTI (mostly Escherichia coli). He presented at 9 years old with gross haematuria and no other symptoms. On ultrasonography a small polypoid bladder lesion (1.5 cm diameter) was found. Cystoscopy confirmed the presence of the lesion, in a diverticulum of the bladder wall, which was completely resected. Histology showed a polypoid lesion with evidence of cystitis cystica and glandularis. Continuous antimicrobial prophylaxis was restored; at 2.5-years of follow-up there was no recurrence.

Patient no. 2 was operated at 16 months old to correct an ectopic megaureter in a duplex kidney. At the follow-up, recurrent UTIs from E. coli and Pseudomonas spp were recorded. He presented at 9 years old with irritative bladder symptoms (frequency, urgency) and an irregular bladder wall on ultrasonography. At cystoscopy a single polypoid bladder mass was found and completely resected. After 2 years the follow-up was uneventful and histology showed cystitis glandularis.

Patient no. 3 was operated at 1 year old to correct a left obstructive megaureter; the recovery was uneventful. At follow-up there was no recurrent UTI reported by the parents and the dilatation of the upper urinary tract recovered almost completely. At 13 years old the annual ultrasonography showed a wide bladder mass (3 cm diameter) on the right lateral bladder wall and smaller multiple lesions on the left side (Fig. 1). At cystoscopy multiple polypoid lesions were found (Fig. 2a,b) and biopsied. Histology showed cystitis glandularis (Fig. 3). The lesion was completely resected by transurethral endoscopy and at the 1-year follow-up there was no recurrence detected.

In all cases the diagnosis was confirmed at histology; specimens were examined during surgery and completely resected endoscopically. Histology showed bladder mucosa with oedematous lamina propria, epithelial hyperplasia and characteristic glandular structures lined with mucus-secreting cubic and columnar cells (Fig. 3).

DISCUSSION

The cause of cystitis cystica glandularis is debatable; the ‘embryological theory’, currently abandoned, considered that the mucus-secreting cells of cystitis glandularis might arise by inclusion of intestinal mucosa in the bladder from the primitive cloaca or from the residue of the omphalo-mesentric duct [1,3,4]. The intestinal metaplasia of cystitis glandularis is a result of a chronic
irritative and infectious stimulus. The initial appearance of submucosal masses of epithelial cells (Brunn's nest) is followed by the cavitation of such structures, from central necrosis or serosal secretion, with the appearance of miliary cystic structures lined with a cubic or columnar epithelium and filled with serosal fluid, termed cystitic cystica. The condition is termed cystitis glandularis when there is metaplasia in a mucus-secreting epithelium [4].

Cystitis cystica may be a common finding in adults and is described in 1.4% of autopsies [4]. The exact incidence of cystitis glandularis is nonetheless unknown. Patients with bladder exstrophy [1], pelvic lipomatosis [7] and chronic or recurrent UTIs, mostly by E. coli, Proteus, Pseudomonas, Klebsiella and Chlamydia, are considered at risk [2–4]. In patients with no UTIs, other causal factors have been proposed, including avitaminosis, allergy, hormone imbalance, specific carcinogens [2] and IgA-mediated immune mechanisms [7].

The lesions of cystitis glandularis are more frequent at the bladder neck or on the trigone, and less common on the lateral bladder walls or on the dome, in the urethra, pelvis and ureter.

The presenting symptoms of cystitis glandularis may be haematuria or irritative symptoms, e.g. frequency, urgency and urinary incontinence, the latter probably a result of the association with diffuse cystitis cystica; in the more florid forms, cystitis glandularis may be discovered as a polypoid mass on ultrasonography, resembling bladder malignancy.

The clinical significance of cystitis glandularis and the correlation with malignant bladder lesions is still debated. The risk of association with bladder cell carcinoma has been reported [2] and an association with bladder adenocarcinoma was reported [8–12]. More recent data seem not to support the premalignant potential of cystitis cystica and cystitis glandularis [3]. While most patients with cystitis cystica and glandularis will never develop a malignant bladder lesion, it cannot be excluded that the most wide proliferative lesions of cystic glandularis may have a premalignant potential in some cases [4].

Data on cystitis cystica and cystitis glandularis in children are scarce. Kaplan and Data on cystitis cystica and cystitis glandularis may have a premalignant potential in some cases [4]. While most patients with cystitis cystica and glandularis will never develop a malignant bladder lesion, it cannot be excluded that the most wide proliferative lesions of cystic glandularis may have a premalignant potential in some cases [4].

In conclusion, cystitis glandularis is infrequently reported in children, and probably represents the reaction of the bladder epithelium to any irritative chronic stimulus, e.g. recurrent UTIs, and may present as a florid polypoid lesion which resembles a bladder malignancy. The diagnosis is by histology and transurethral resection of the lesion is generally the only treatment required. The risk of recurrence and a possible premalignant potential cannot be excluded, and suggests periodic monitoring with bladder ultrasonography and cystoscopy.

CONFLICT OF INTEREST

None declared.

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Inhibition of Ki–67 in a renal cell carcinoma severe combined immunodeficiency disease mouse model is associated with induction of apoptosis and tumour growth inhibition

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OBJECTIVE

To evaluate the effects of suppressing the expression of Ki–67 (expressed in proliferating cells) by antisense oligonucleotides (asON) directed against Ki–67 (which specifically inhibit the proliferation of tumour cells and tumour growth in cell culture and in subcutaneous murine tumour models) on the growth, cell viability and angiogenic activity of a preclinical renal cell carcinoma (RCC) severe combined immunodeficiency disease (SCID) mouse model.

MATERIALS AND METHODS

Human RCC cells (SK-RC-35) were incubated with asON and control ON in the presence of a cationic lipid in monolayer cell culture. To test Ki–67 as a target for antitumour therapy in more complex models, asON were administered to three-dimensional RCC (SK-RC-35) spheroid cultures and to SCID mice bearing subcutaneous SK-RC-35 xenografts. For animal studies, $1 \times 10^6$ SK-RC-35 cells were implanted subcutaneously. Subsequently, asON or ON were injected intraperitoneally daily for 14 days at 10 mg/kg/day. Tumour size, weight and status of metastasis were documented daily and after death, respectively. The number of apoptotic cells, Ki–67-positive cells and the microvessel density in tumour sections was determined immunohistochemically. Quantitative reverse transcription-polymerase chain reaction of Ki–67 mRNA was also assessed for the tumours.

RESULTS

Treatment of RCC cells with asON resulted in a specific inhibition of cell growth in monolayer and spheroid cell culture. Systemic administration of Ki–67-directed asON significantly decreased tumour growth ($P=0.009$) in SCID mice.

CONCLUSION

These results indicate that Ki–67 represents a suitable antiproliferative target, and that asON are a potent agent inhibiting tumour growth and apoptosis, but not tumour vascularization, in human RCC.

KEYWORDS

Ki–67, antisense, renal cell carcinoma, molecular therapy, proliferation

INTRODUCTION

The Ki–67 antigen is widely known as an appropriate and useful marker of the proliferating fraction within a given cell population. Estimating the growth fraction by measuring Ki–67-positive cells in tissue sections serves as an independent prognostic marker for human RCC in multivariate analyses [1–3]. The mean immunohistochemical Ki–67 index correlates with tumour grade and is 6.2–13% (total range 0–60%) in different studies, while the fraction of Ki–67-positive cells in benign renal tissue is generally <1% [1–4]. As Ki–67 expression in kidney tumours correlates with the patient outcome, and as cell proliferation correlates with the Ki–67 labelling index, Ki–67 protein expression might be a promising target for a causative therapeutic treatment of RCC.

Several reviews have detailed the oncological prognostic value of Ki–67 labelling in different tumours, and the potential cellular function [5,6]. For functional aspects a role for Ki–67 protein in the control of higher-order chromatin structure has been described recently [7].

Antisense oligonucleotides (asON) are designed to specifically hybridize with complementary target mRNA and to inhibit gene expression through various mechanisms, e.g. enzymatic cleavage of the targeted RNA strand by RNase H, translational arrest inhibition or inhibition of mRNA processing, maturation and transport [8,9]. Thus, asON serve as a tool and a potential agent to suppress malignant gene expression.

Currently there are no effective treatment options for metastatic RCC; this tumour is widely chemo- and radio-resistant, and responses to immunotherapy are poor. As kidneys have a high uptake and local accumulation of phosphorothioate oligonucleotides [9], sufficiently high local concentrations may be expected to affect target gene expression. Therefore, RCC is a tumour for which therapeutic strategies in...
the use of asON seem to be promising. Previously we showed that Ki-67-directed asON inhibit Ki-67 mRNA and protein expression, induce apoptosis in vitro, and effectively inhibit tumour growth in syngeneic murine bladder, prostate and renal cell cancer animal models [10,11].

Thus, in the present study we evaluated the effects of asON-mediated suppression of Ki-67 expression on the growth, cell viability and angiogenic activity of a highly relevant preclinical RCC SCID mouse model at a more mechanistic level.

MATERIALS AND METHODS

Human SK-RC-35, -47 and -58 RCC cell lines were originally established from primary nephrectomy specimens from patients with RCC [12]. Cells were cultured in RPMI-1640 (Invitrogen, Karlsruhe, Germany), 1% sodium pyruvate, 10% fetal calf serum, 1% l-glutamine, 10 U/mL penicillin and streptomycin (Biochrom, Berlin, Germany). Cells were maintained at 37 °C in a 5% CO₂, humidified incubator. To evaluate cell numbers after ON transfection, 5 × 10⁵ cells were seeded in 96-well plates; after 24 h the cells were treated with ON (360 nmol/L) in the presence of Tfx and cells were counted after 48 h of incubation with asON, sense ON or nsON sequences, or Tfx only. The ON were directed against the human Ki-67 start codon region at position 197–219 (Exon 2); the ON were purified by HPLC. The sequences used were: antisense: 5′-ACC AGG COT CTC GTG GGC CAC AT-3′; sense: 5′-ATG TGG CCC ACG AGA CGC CTG GT-3′; and nonsense: 5′-AGT ACT CAG TAA CGC CTA CGG TAA G-3′.

To determine Ki-67 mRNA expression, total RNA in tumours was prepared using the Qiagen RNeasy Kit (Qiagen). Cells were cultured in RPMI-1640 culture were injected in 100 µL media subcutaneously into 5–6-week-old CB17 SCID mice (Charles River, Sulafeld, Germany). Beginning 24 h later, ON were injected every day intraperitoneally at 10 mg/kg/day for 14 days, until at 22 days the mice were killed. Three treatment groups received either asON, nonsense ON (nsON) or medium, and each group included at least five animals. One mouse each in the asON and nsON groups had no tumour take. Tumours were measured with a calliper every other day and tumour volumes calculated as \( \pi/6 \times b^3 \), where \( a \) was the longest and \( b \) the shortest tumour diameter. After death the xenograft tumours were weighed and subsequently fresh-frozen in liquid nitrogen. The results were analysed statistically using the rank-sum Mann-Whitney test. The animal studies were approved by the institutional and governmental review boards, with animals killed if the maximum tumour diameter was \( \geq 1 \) cm.

RESULTS

Antiproliferative effects of Ki-67 asON in monolayer cell culture were recorded in 96-well plates. The SK-RC-35 cells were transfected at an ON concentration of 360 nmol/L in the presence of Tfx and cells counted after 48 h of incubation with asON, sense ON or nsON sequences, or Tfx only. The asON treatment resulted in a marked inhibition of cell proliferation, with about half the number of cells than in the negative control with Tfx only. Cell growth was not influenced significantly by treatment with control ON (Fig. 1). SK-RC-35 cells were counted (MVC) at x 50 under light microscopy.
Antiproliferative effects of Ki-67 asON in human RCC spheroid culture; asON (light green closed squares), nsON (red closed squares), medium (green closed circles) and sense ON (green open circles). a, The growth curve is for SK-RCC-35 spheroids; ON were applied once (day 0) and each point represents the mean (SD) of triplicate measurements. b, Shows phase-contrast views of spheroids at 12 days after treatment, with representative asON- and nsON- treated spheroids.

Antitumoral effects in SCID mice with subcutaneous RCC tumours. Three treatment groups received either daily intraperitoneal asON (light green closed squares), nsON (red closed squares) or medium (green closed circles) injections from day 1–15. After 22 days the mice were killed, and the plots show the mean (SD) tumour volume changes with time.

To determine the effects of Ki-67 asON treatment on tumour growth in vivo, SK-RCC-35 tumour cells were injected subcutaneously into SCID mice and three groups received either daily intraperitoneal asON, nsON or medium injections. ON were applied at 10 mg/kg/day for 14 days, beginning 1 day after tumour cell injection. After 22 days the mice were killed and tumour volumes measured. Growth was much less in asON-treated tumours than in the control groups (Fig. 3). Tumour weights when the mice were killed confirmed growth inhibition, with statistically significantly lower weights in the asON, at 58.5 (19.8) mg, than in the medium, at 201 (30) mg (P = 0.009 rank-sum Mann–Whitney) and the nsON controls, at 168.8 (100.2) mg (P = 0.05). The difference in tumour weights between the nsON and medium groups were not significant (P = 0.26).

After death about half of each tumour was used for RNA preparation and quantitative Ki-67-specific RT-PCR analysis; Ki-67 mRNA copy numbers were normalized to glyceraldehyde-phosphate dehydrogenase-specific RNA. Results showed an enhanced mean Ki-67 mRNA expression in asON-treated tumours which was 137.8 (15.7)% of the Ki-67 mRNA expression in medium-treated controls. Results after nsON, at 100.9 (25.7)% of medium-treated tumours and medium administration were almost identical.

The second half of the tumours was frozen and used for immunohistochemical analysis of Ki-67 antigen, activated caspase 3, and CD31 antigen. Ki-67 staining with the MIB-1 antibody showed a marked reduction of Ki-67-positive cells in the asON (27.8%) which was almost significant (P = 0.057, Mann–Whitney) compared to the control groups with nsON (42.5%) and medium treatment (57%). Figure 4a,b show representative labelling of asON and nsON-treated tumours, respectively, with a significantly lower Ki-67-positive fraction after asON treatment.

Apoptotic cells in tumour sections were analysed by staining activated caspase 3, a well established method for analysing the apoptotic fraction. Caspase 3 is an essential early effector of apoptosis. Activated caspase 3 staining showed markedly more positive cells in the asON group (3.72%) that was almost significant (P = 0.057, Mann–Whitney) than in the control groups with nsON (1.82%) and medium (1.58%). Figure 4c,d shows representative labelling of the asON- and nsON-treated tumours, respectively.

To visualize blood vessels in tumours the CD31 antigen was stained immunohistochemically; the MVC at ×50 revealed only minor differences between the asON (25.1 counts, Fig. 4e) and the nsON (28.3, Fig. 4f) or medium groups (20.7, P = 0.23 Mann–Whitney. Figure 4e,f show representative views of asON- and nsON-treated tumours, respectively, with no obvious difference in MVC.
DISCUSSION

Immunolabelling of the Ki-67 antigen is a well known prognostic marker for patient outcome for many tumour types. In addition to the histopathological value, Ki-67 expression is a promising target for causative therapeutic treatment of different tumours. In syngeneic animal models with subcutaneous or orthotopic bladder, prostate, or RCC tumours, there is significant Ki-67 asON-induced tumour growth inhibition [10,11]. Based on these findings, a clinical phase I study has been initiated where patients with bladder carcinoma are treated intravesically with Ki-67 asON.

Molecular *in vitro* analysis showed that the reduction of Ki-67 mRNA and protein using asON results in apoptotic cell death [10]. These effects were related to levels of Ki-67 protein expression. Thus, it was assumed that cells entering mitosis in the absence of Ki-67 protein are unable to complete the process and are forced into apoptosis. These findings prompted us to evaluate the combined treatment of tumour cells with Ki-67-derived asON and conventional chemotherapy. However, preliminary data indicate that asON do not enhance chemosensitivity, probably because of the inhibition of tumour cell proliferation, which is a prerequisite for many chemotherapeutic agents.

The present SCID mice experiments confirmed significant asON-induced antitumoral effects in a clinically more relevant animal model, and furthermore showed that Ki-67 target protein expression and to a lesser extent induction of apoptosis (which were shown previously *in vitro*) also occur *in vivo* after asON treatment. Thus, it was possible to gain mechanistic insights into the *in vivo* situation.

It was hypothesized that Ki-67 asON may not only interfere with proliferating tumour cells but also with endothelial cells, and may thus influence tumour neoangiogenesis. The current experiments showed that microvessel staining in tumours was not significantly influenced after asON treatment when compared to control treatment. Therefore, it seems that the observed antitumoral effects are, at least in this model, not mediated by inhibition of neoangiogenesis.

We showed previously in human monolayer cell culture that the transfection with Ki-67 asON resulted in mRNA and protein down-regulation, indicating an RNaseH-dependent mechanism [10]. However, in these *in vivo* experiments there was significant down-regulation of Ki-67 protein immunohistochemically in asON-treated tumours but not of Ki-67-mRNA. Others showed in mice that *in vivo* phosphothioate ON are cleared from plasma biphasically within 50 min and 40 h, and 70% of a bolus administration is excreted within 10 days [17]. We assume that the time of death, at 7 days after the end of treatment, was too late to detect ON-induced effects on mRNA expression. Perhaps the effects on apoptosis and Ki-67 protein expression would also be more significant when tumours are harvested directly after or during treatment. Therefore, effects on target gene and protein expression, and cell viability, must be assessed at different times during therapy in detailed future studies including long-term treatment and survival analysis. If future experiments confirm these promising data, Ki-67 asON treatment may indeed be an interesting therapeutic tool for clinically treating RCC.

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CONFLICT OF INTEREST
None declared.

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Abbreviations: SCID, severe combined immunodeficiency disease; (as) (ns) ON, (antisense) (nonsense) oligonucleotide; MVC, microvessel count; Tfx, transfection medium.
Anti-tumour activity of heat-shock protein 60-recognizing CD4+ T cells against syngeneic murine renal cell carcinoma

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INTRODUCTION

Recent advances in tumour immunology have identified several tumour antigens, enabling patients with cancer to be treated with specific immunotherapy [1,2]. Peptides derived from either cancer-testis antigens and melanocyte-differentiation antigens have been used for specific immunotherapy against melanomas, with clinical responses reported [3,4]. Several tumour antigens expressed on RCC cells have been identified, including mutated antigens from either cancer-testis antigens [5] or heat-shock protein (HSP) 70–2 [6], but these are patient-specific mutated antigens. Potentially shared antigens, including RAGE-1 [7], intestinal carboxyl esterase [8], G250 [9], and fibroblast growth factor-5 [10] have also been reported, but their usefulness for immunotherapy against RCC has not been determined.

HSPs are highly conserved molecules that act as chaperones involved in the folding of newly synthesized proteins [11,12]. Recently, the stimulatory capacity of HSP-60 on the innate immune system has been recognized, and HSP-60 was suggested to act as a ‘danger signal’ for the innate immune system [13]. HSP-60 also stimulates T cells [14], induces maturation of dendritic cells, and promotes T helper type 1 (Th1)-type T cell responses [15,16]. In addition, HSP is induced in cells by various stressors, including transformation, and different types of tumour cells express several types of HSP [17–19]. We previously reported that HSP-60-recognizing Th1 type CD4+ T cells can show antitumour activity against HSP-60-expressing fibrosarcoma cells [20]. In the present study, we examined the expression of HSP-60 in a RCC line (RENCA cells) and determined whether HSP-60-recognizing CD4+ T cells could show antitumour activity against them.

MATERIALS AND METHODS

Female BALB/c (H-2d) mice (8–10 weeks old) were purchased from Japan SLC (Shizuoka, Japan). All mice were bred in specific pathogen-free conditions. We generated an autoreactive HSP-60-recognizing CD4+ T cell clone from lymph-node cells of naive BALB/c mice [14], and a T cell clone BASL1.1 was established by the limiting-dilution technique, as described previously [20]. RPMI 1640 (Gibco, Grand Island, NY) supplemented with 10% heat-inactivated fetal calf serum (HyClone, Logan, UT), 50 μmol/L 2-mercaptoethanol, 20 mmol/L 4-(2-hydroxyethyl)-1-piperazineethanesulphonic acid, 30 μmol/L gentamicin (Schering Corporation, Kenilworth, NJ), and 0.2% sodium bicarbonate was used as the complete culture medium.

RENCA is a renal cortical adenocarcinoma cell line of BALB/c origin; this tumour line was maintained in vitro in the complete culture medium and confirmed to be mycoplasma-free (Flow Laboratories, McLean, Virginia). The antitumour activity of BASL1.1 was assayed by the modified Winn’s technique [21]. Briefly, RENCA cells (5 × 10⁶) were injected subcutaneously into the right abdomen with or without BASL1.1 cells (2 × 10⁶) in 0.2 mL. As a control, RENCA cells were co-inoculated with whole lymph-node cells (2 × 10⁶) from naive BALB/c mice. Each group consisted of five mice. After tumour inoculation, tumour...
growth was inspected every 3 or 4 days by measuring the largest perpendicular diameters, and recorded as tumour area (mm²). Tumour acceptance was finally determined after 30 days. In some experiments the RENCA tumours were removed 20 days after tumour inoculation in each group, and fixed in 10% buffered formalin, embedded in paraffin, and 5-μm sections cut and stained with haematoxylin and eosin.

Expression of MHC class I and II, and HSP-60, on RENCA cells was analysed by FACScan (Becton Dickinson, Mountain View, CA) as follows. The RENCA tumour cells were incubated in the complete medium supplemented with 5% rabbit serum to block the Fc receptor for 15 min. Fluorescein isothiocyanate (FITC)-conjugated anti-H-2Kd monoclonal antibody (mAb, mouse IgM; Meiji Institute of Health Science) was used for analysing MHC class I expression. The staining background was determined by treatment with no antibody. For the expression analysis of MHC class II and HSP-60 on the cell surface, the RENCA tumour cells were treated with anti-I-A\(^d\) mAb (mouse IgG2a; Meiji Institute of Health Science) or anti-HSP-60 mAb (ML30; kindly provided by Dr J. Ivanyi, Royal Postgraduate Medical School, London), which recognises both mycobacterial and murine HSP-60 [22], for 30 min at 4 °C. These cells were then stained with FITC-labelled affinity-purified F(ab\(^{-}\))\(^2\) fragments of antimouse IgG (Tago, Inc), and then analysed by FACScan. Data were displayed as histograms on a logarithmic scale. The staining background was determined by the secondary antibody alone. For intracellular staining, the RENCA tumour cells were pre-fixed with paraformaldehyde before blocking the Fc receptor. Statistical significance was determined using Student's t-test, with P < 0.05 considered to indicate significance.

RESULTS

The expression of MHC on RENCA cells is shown in Fig. 1; flow cytometry showed that the RENCA cells were positive for H-2Kd but negative for I-A\(^d\) molecules. There was no staining of anti-HSP-60 mAb when RENCA cells were stained with no pretreatment, but RENCA cells were stained with the mAb when pre-fixed with paraformaldehyde to permeabilize the cell membranes, indicating that RENCA cells express intracellular HSP-60.

We then determined whether an autoreactive and HSP-60-recognizing CD4\(^+\) T cell clone, BASL1.1, could show in vivo antitumour activity against RENCA cells. This T cell clone can produce Th1-type cytokines [20]. RENCA cells were inoculated subcutaneously with or without BASL1.1 cells or naive lymph node cells, and tumour size estimated kinetically. The growth of RENCA was significantly suppressed when RENCA cells were co-incubated with BASL1.1 cells (Fig. 2), but there was no growth suppression when RENCA cells were co-incubated with whole lymph-node cells from naive BALB/c mice. The tumour acceptance at 30 days showed that three of the five mice rejected RENCA cells when co-incubated with the BASL1.1 cells. By contrast, all five BALB/c mice accepted the challenged RENCA cells when co-incubated with or without naive lymph-node cells.

To further evaluate the mechanisms by which BASL1.1 cells suppress the growth of RENCA, we assessed the histopathology of the tumours 20 days after tumour inoculation in each group. In the RENCA tumours co-incubated with BASL1.1 cells there was diffuse infiltration of mononuclear cells around the tumour cells (Fig. 3a), but in tumours co-incubated with whole lymph node cells from naive BALB/c mice there was only a mild infiltrate of mononuclear cells (Fig. 3b).

DISCUSSION

HSPs have diverse roles in cell biology and the immune system; some groups of HSP are related to urological cancers [23], and two small HSPs, \(\alpha\)B crystalline and HSP-27, increase in human urological tissues [24]. In addition, HSP-72 is expressed in RCC and its expression has been suggested to have prognostic implications [25]. Although we did not examine the expression of HSP-60 in the tumour tissue we showed that the RENCA cell...
In addressing the mechanism of antitumour immunotherapy against urological cancer, we suggest that HSPs can be target molecules in activity against RENCA cells. These results against murine fibrosarcoma [20], and in the cells, through recognition of HSP-70 by MHC-restricted manner [26,27]. In addition, HSP-70 on human sarcoma cells in a non-immunogenic determinant associated with natural killer cells recognize a heat-inducible expressed intracellular HSP-60.

Recent advances in tumour immunology have resulted in the identification of several tumour antigens [1,2]. Most human tumour-associated antigens characterized to date are derived from unmutated self-proteins. Indeed, unmutated melanocyte differentiation antigen-derived peptides have been used for specific immunotherapy in patients with melanoma, with clinical responses reported [3,4]. In addition, both p53 and Her2/neu are thought to be good target molecules for specific immunotherapy against cancer, despite their expression in normal cells [31]. These lines of evidence indicate that antitumour immune responses could be considered as an anti-self immune response to tumour cells, as reported previously [32,33].

In the present study, we administered autoreactive and HSP-60-recognizing CD4+ T cells locally, but there was no autoimmune symptom in the treated mice (unpublished observation). Based on the idea that the impairment of antitumour immune response might be a lack of a local accumulation of T cells and a deficiency in their production of cytokines, local transfer of HSP-60-recognizing CD4+ T cells might be useful for treating patients with various types of cancer.

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CONFLICT OF INTEREST
None declared.

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Natural killer cells recognize a heat-inducible immunogenic determinant associated with HSP-70 on human sarcoma cells in a non-MHC-restricted manner [26,27]. In addition, there can be autologous tumour killing induced by heat treatment of fresh tumour cells, through recognition of HSP-70 by γδ T cells [28]. Furthermore, human tumour-infiltrating CD4+ T cells can show reactivity to B cell lines that express HSP-70 [29]. We previously reported that HSP-60-recognizing CD4+ T cells can show antitumour activity against murine fibrosarcoma [20], and in the present study such T cells also had antitumour activity against RENCA cells. These results suggest that HSPs can be target molecules in immunotherapy against urological cancer.

In addressing the mechanism of antitumour activity of the BASL1.1 cells, we propose the following hypothesis. BASL1.1 cells recognize HSP-60-derived peptides in the context of I-Aγ molecules on self-antigen-presenting cells, and produce Th1 type cytokines. Importantly, CD4+ BASL1.1 cells cannot respond to MHC class II negative RENCA cells. As a consequence, the local secretion of interferon-γ and interleukin-2 results in accumulation of macrophages and cytotoxic T lymphocytes, as is the case with fibrosarcoma [20]. Indeed, there was significant infiltration of mononuclear cells around the tumour cells in the RENCA tumour co-inoculated with BASL1.1 cells. There was only a mild infiltrate of mononuclear cells in the tumour co-inoculated with whole lymph node cells from naïve BALB/c mice (both × 120).


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Abbreviations: RENCA, renal adenocarcinoma; HSP, heat shock protein; Th1, T helper type 1; mAb, monoclonal antibody; FITC, fluorescein isothiocyanate.
Evaluation of hypoxia-inducible factor 1α overexpression as a predictor of tumour recurrence and progression in superficial urothelial bladder carcinoma

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OBJECTIVES
To investigate the possible role of hypoxia-inducible factor 1α (HIF-1α, a transcription factor important in regulating O2 homeostasis and physiological responses to oxygen deprivation) in the recurrence and progression of superficial urothelial bladder cancer, and to examine its expression in relation to proliferation status, apoptotic activity and intratumoral angiogenesis.

PATIENTS AND METHODS
Paraffin wax-embedded tissue from 140 patients with superficial primary urothelial bladder carcinoma was immunostained for HIF-1α, Ki-67, single-stranded DNA antibody for apoptotic cells, p53, bcl-2, vascular endothelial growth factor and CD31 antigen. We calculated the proliferative rate, the apoptotic index and the microvessel density (MVD). The mean (SEM) follow-up was 46 (3.5) months, within which 86 patients relapsed while 18 progressed to a higher tumour stage and/or grade.

RESULTS
HIF-1α expression was more common in high-grade superficial urothelial carcinomas. The positivity was related to increased proliferative activity (P = 0.012), apoptotic rate (P = 0.006) and MVD (P < 0.001). HIF-1α overexpression had a marginal adverse influence on progression-free survival (P = 0.058; univariate analysis), but when combined with p53 overexpression, the unfavourable impact was statistically important (P = 0.028). In multivariate analysis, only grade and the high Ki-67 labelling index were significant predictors of recurrence-free survival, while T-stage and the HIF-1α/p53+ phenotype emerged as the only independent variables of adverse prognostic significance for time to progression.

CONCLUSIONS
HIF-1α overexpression combined with aberrant mutant p53 nuclear protein accumulation seem to indicate an aggressive phenotype, suggesting a potential biological model predictive of future risk of disease progression in patients with superficial urothelial bladder carcinoma. These indicators may be helpful in clinical practice to discriminate superficial bladder cancer worth a more intensive follow-up, or more aggressive treatment.

KEYWORDS
urothelial bladder carcinoma, hypoxia, angiogenesis, apoptosis, recurrence, progression

INTRODUCTION
Most (70–90%) newly diagnosed urothelial carcinomas (UCs) of the bladder are superficial (confined to the mucosa, i.e. Ta, or subepithelial layer, T1). However, after the initial management, about two-thirds of patients with these tumours will develop recurrent disease, while 15–30% will progress to a higher stage and/or grade [1]. If the prognosis of an individual patient could be predicted earlier in the course of the disease, those with a high likelihood of recurrence or progression could be treated more aggressively. The traditional criteria of histological grade, stage, size and multiplicity cannot accurately predict the probability of recurrence or progression of superficial bladder UCs. Although many markers have been proposed to identify patients who will follow a more aggressive course, until now no reliable method of determining the risk of recurrence or progression in those patients has been developed.

The need to identify which patients are at risk of subsequent relapse or progression has provoked intense research into the molecular mechanisms of growth control in bladder cancer. The prognostic role of intratumoral hypoxia has not been defined, although various studies suggested the significance of cellular adaptation to hypoxia and tumour neovascularization in the development of invasive disease in various solid tumours [2,3]. Hypoxia-inducible factor 1 (HIF-1) is a heterodimeric transcription factor that regulates O2 homeostasis and physiological responses to O2 deprivation [2,4,5]. HIF-1 consists of two subunits, HIF-1α and HIF-1β, that belong to a subfamily of basic-loop-helix transcription factors containing a ‘Per-ARNT-Sim’ motif [6]; HIF-1α is the unique, O2-regulated subunit that determines HIF-1 activity [4]. A decrease in cellular O2 tension leads to increased HIF-1 activity via stabilization and accumulation of the HIF-1α protein; conversely, ubiquitin-mediated proteolysis of HIF-1α on re-exposure to a normoxic environment results in the rapid decay of HIF-1 activity [4,6]. The binding of
HIF-1 to hypoxia-response elements of DNA leads to the transcriptional activation of a battery of genes which are responsible for the metabolic switch to glycolysis for energy production, anaerobic metabolism, haematopoiesis, angiogenesis, vasodilatation and iron metabolism, all of which are implicated in the basic biology of cancer [4,5,7].

The aim of the present study was to determine the effect of HIF-1α protein expression on the prognosis [recurrence or progression] of superficial urothelial bladder cancer, and its correlation with the dependent cell-cycle regulator p53, the anti-apoptotic protein bcl-2, the Ki-67 labelling index, the apoptotic rate and the angiogenesis markers vascular endothelial growth factor (VEGF) and microvessel density (MVD).

PATIENTS AND METHODS

From 1993 to 2003, 140 patients presenting at the authors’ institutions with newly diagnosed primary superficial UC of the urinary bladder had a complete transurethral resection (TUR). The mean (median, range) age of the patients (107 men and 33 women) was 69 (68, 23–89) years. The cohort was not entirely consecutive because of inadequate tumour tissue for immunohistochemistry in some superficial small tumours. In addition, patients with incomplete medical records or inadequate follow-up, those with a history of bladder biopsy for any reason before the primary surgery, and specimens with moderate to severe inflammation on histological evaluation were excluded from study, allowing the determination of the angiogenic phenotype to be free of iatrogenic or other confounding factors. The tumours, according to the TNM classification, comprised 42 Ta and 98 T1 UCs; they were graded using the WHO criteria. The tumours, according to the TNM classification, comprised 42 Ta and 98 T1 UCs; they were graded using the WHO criteria. The histological stage and grade were evaluated jointly and a consensus reached. The tumours, according to the TNM classification, comprised 42 Ta and 98 T1 UCs; they were graded using the WHO criteria. The patients were assessed by urine cytology and cystoscopy every 3 months for the first 2 years after the first resection, every 6 months for the next 2 years, and yearly thereafter, if there was no recurrence. The mean (SEM, median, range) follow-up for the whole series was 46 (3.5, 41, 8–131) months. The tumour recurred in 86 (61.5%) patients, while 18 (13%) progressed to a higher tumour stage and/or grade. After the initial TUR, tissues were fixed in 10% buffered formalin and then embedded in paraffin wax.

IMMUNOHISTOCHEMISTRY

All samples were immunohistochemically stained using the standard three-step streptavidin-peroxidase technique, as previously described [2,8–12]. The following antibodies were used: (i) mouse monoclonal antibody against HIF-1α (StressGene, Victoria, British Columbia, Mab H1α7, IgG1 isotype, diluted 1 : 1200, microwave pretreatment, overnight incubation); (ii) MIB-1 for Ki-67 (VLEM, Rome, Italy, purchased pre-diluted, microwave pretreatment, 1 h); (iii) F-7–26 for single-stranded DNA (Lexis Corp., San Antonio, TX, diluted 1 : 10, 15 min); (iv) DO-1 for p53 (Oncogene Science, Uniondale, NY, diluted 1 : 80, 1 h); (v) bcl-2, clone 124 (Dako, Carpinteria, CA, diluted 1 : 100, microwave pretreatment, 1 h); (vi) purified mouse anti-human VEGF Mab (IgG1, isotype, clone G153-694, PharMingen, SanDiego, CA, diluted 1 : 75, microwave pretreatment, overnight incubation) recognizing the 165, 189 and 206 isoforms of VEGF; and (vii) murine monoclonal anti-Cd31 antibody clone J70A (IgG1 kappa isotype, Dako, Denmark, diluted 1 : 50, microwave pretreatment, overnight incubation). Positive and negative controls were also stained in each run.

Staining for all antibodies was assessed while unaware of the clinical data by two assessors; whenever there was a difference of >10% between the assessors, slides were reviewed jointly and a consensus reached. The evaluations agreed in >90% of the samples for all markers. A minimum of five randomly selected fields throughout the whole section at ×400 magnification was examined, except from microvessel counting, where the ‘hotspot’ method was used [11,12].

The assessment of HIF-1α was based on previously described guidelines [13]. Tumour cell immunoreactivity for HIF-1α was scored according to the nuclear staining. Both the percentage of positively stained tumour cells and the staining intensity were considered to determine the expression of HIF-1α. The percentage of positive cells was rated as: 1 point, ≤10% positive tumour cells; 2 points, 11–50%; 3 points, 51–80%; and 4 points, ≥81%. The staining intensity was rated as: 1 point, weak intensity; 2 points, moderate intensity; and 3 points, strong intensity. Points for expression and percentage of positive cells were added and specimens ascribed to four groups according to their overall score: absent nuclear immunostaining, ≤10% of cells stained positive; regardless of intensity; weak nuclear immunostaining, 3 points; moderate nuclear immunostaining, 4–5 points; and strong nuclear immunostaining, 6–7 points. For statistical reasons, tumours were then scored using a two-scale system, i.e. low reactivity, denoting tumours with absent or weak nuclear immunostaining, and high reactivity, tumours with moderate to strong nuclear reactivity.

The anti-single-stranded DNA monoclonal antibody was used for quantifying apoptotic cell death [8]; this antibody recognises exposed single-stranded regions in the DNA of apoptotic cells during heating. The apoptotic index (AI) was calculated as the percentage of cancer cells with anti-single strand DNA to the total number of carcinoma cells counted [8]. The proportion of cells showing any nuclear reactivity for Ki-67 was used to calculate the Ki-67 labelling index (LI), providing a measure of the growth fraction [9]. Tumours expressing p53 in >10% of tumour nuclei were regarded as positive, while bcl-2 reactivity was scored positive if >10% of tumour cells showed distinct cytoplasmic staining [8].

The intratumoural angiogenesis was assessed by the immunohistochemical expression of the angiogenic factor VEGF and the determination of MVD. The percentage of cancer cells with cytoplasmic VEGF reactivity was recorded to assess VEGF reactivity. The median value was used as a threshold to define tumours with high and low reactivity for VEGF. The method used to measure MVD was very similar to that of Weidner et al. [11] and other modifications already applied in other similar studies [10,12]. Microvessels were identified by immunostaining of endothelial cells with anti-Cd31 monoclonal antibody, which recognises the CD31 endothelial glycoprotein (platelet/endothelial cell adhesion molecule–1). Many investigators have used anti-vWF antibody, a pan-endothelial marker, to quantify tumour MVD.
The results were assessed statistically using Student’s t-test or one-way ANOVA and the chi-square test were used for testing correlations between continuous tumour variables (comparison of the mean values from two or more sets of data) and categorical tumour variables (contingency tables), respectively. Bivariate associations between ordinal variables was assessed using Spearman’s rank correlation. Survival curves were plotted using the method of Kaplan and Meier, and the significance of observed differences assessed with the log-rank test. Survival was analysed using first recurrence and progression as the endpoints for recurrence-free and progression-free survival, respectively. The first was defined as the time from the end of primary surgery until the first evidence of recurrence of disease with cystoscopy and biopsy. Progressive disease was defined as a relapse at a higher pathological grade and/or more advanced tumour stage. In the univariate analysis the continuous variables were categorized using the median value. The effect of various variables on outcome was investigated by multivariate analysis using the Cox proportional hazards model. For all tests, \( P \leq 0.05 \) was considered to indicate statistical significance.

**RESULTS**

HIF-1α expression was detected as nuclear staining of positive cells (Fig. 1). There was low reactivity for HIF-1α in 66 (47%) and high reactivity in 74 (53%) of the samples. The normal urothelium was negative for HIF-1α. Tumour cells also had very weak cytoplasmic HIF-1α expression. Over-expression of HIF-1α was detected in the poorly differentiated superficial UCs, but this association was of marginal statistical significance (\( P = 0.06 \)). There was no significant association between HIF-1α expression and histological stage (Ta vs T1; \( P = 0.17 \)). In some specimens, HIF-1α was detected in tumour cells that were close to areas of necrosis and away from the blood vessels; however, most tumours had a diffuse pattern of immunohistochemical nuclear staining, in which tumour cells both immediately next to patent blood vessels and far from them stained intensely. There was tumour-adjacent mucosa with in situ carcinoma in nine cases; most of these areas were also characterized by strong HIF-1α immunoreactivity.

The mean (53m, median, range) Ki-67 LI was 12.8 (1.28, 8.6, 0.6–56%)%; there was a significant positive correlation between Li and tumour grade (\( P = 0.004 \)), but the difference was only marginally significant for tumour stage (\( P = 0.07 \); Table 1). No apoptotic cells could be identified in the normal bladder. Labelled cells were randomly scattered with no obvious polarity towards the basal lamina or outer transitional epithelial layers. The AI increased with increasing grade (\( P < 0.001 \)) and stage (Ta vs T1; \( P = 0.02 \)).

There was positive nuclear staining for p53 in 60 (43%) tumours, and a significant association between p53 positivity and T1 stage (\( P = 0.048 \)) and poor grade (\( P = 0.029 \)). The bcl-2 expression was localized in the cytoplasm and on the nuclear envelope of the urothelial cells. In 46% of the specimens, bcl-2 protein was expressed in the basal cell layers and in 16% other than basal cells. The basal-cell expression pattern was more common in well-differentiated UCs. In the remaining positive cases (38%), both staining patterns were present and was heterogeneous, in which bcl-2 immunoreactive cells showed a random distribution throughout the cancerous epithelium. In adjacent morphologically normal urothelium present in 45 cases, bcl-2 expression was restricted to basal cell layers. Infiltrating stromal lymphocytes were always strongly bcl-2 positive and, along with normal basal layer cells, served as internal positive controls. The mean (53m) percentage of bcl-2 positive cells was 16.4 (2.24). The intensity of positive immunostaining was weak in 20 (22%), moderate in 23 (25%) and intense in 49 (53%) of the 92 positive cases. There was overall bcl-2 positivity in 92 (66%) cases and it was not associated with grade (\( P = 0.40 \)) or T-stage (\( P = 0.33 \); Table 1).

There were statistically significant associations of VEGF expression with advanced tumour stage (Ta vs T1; \( P = 0.03 \)) and grade (\( P = 0.05 \)). MVD also correlated significantly with tumour grade (\( P < 0.001 \)); the correlation of MVD with T-stage was marginal (\( P = 0.064 \); Table 1).

AI was directly correlated significantly with HIF-1α expression (\( P = 0.006 \); Table 1) and there was a relationship of HIF-1α with the proliferation rate of the tumours (\( P = 0.012 \)), but no significant correlation of p53 or bcl-2 expression and HIF-1α (\( P = 0.15 \) and 0.37, respectively). There was no correlation between VEGF expression and HIF-1α expression (low vs high reactivity; \( P = 0.17 \), t-test). Tumours with high reactivity for HIF-1α had a higher mean MVD, at 18.13 (1.03) than those with a low reactivity, at 12.42 (0.98) (\( P < 0.001 \)).

In the univariate analysis, the advanced grade, an increase in Ki-67 LI, VEGF overexpression, p53 positivity and presence of bcl-2 expression indicated a lower recurrence-free survival (Table 2). For progression-free survival, only T-stage, VEGF overexpression
and p53 protein accumulation were statistically significant prognosticators in the univariate analysis, with HIF-1α overexpression of borderline significance (P = 0.058) (Fig. 2A). HIF-1α expression had no influence on recurrence-free survival of the patients with superficial UC (P = 0.28). In 36 of 140 patients (26%) there was both high reactivity of HIF-1α and p53-positivity. Kaplan-Meier analysis (log-rank test) showed a significant unfavourable influence of the combination of HIF-1α high reactivity and p53 overexpression on progression-free survival (P = 0.028) (Fig. 2B). In the proportional-hazard model, only grade and the high Ki-67 LI retained their significance for recurrence-free survival (Table 2). In the multivariate analysis of progression-free survival, T-stage and the HIF-1α+/p53+ phenotype emerged as the only independent variables of adverse prognostic significance.

**DISCUSSION**

Current reports suggest that superficial bladder cancer is a heterogeneous spectrum of diseases with different biological and clinical behaviour, determined by distinct molecular alterations [15]. Although the current clinicopathological classification provides some estimate of the biological potential of superficial disease, significant tumour heterogeneity remains within prognostic subgroups. To identify the intrinsic biological behaviour of the neoplasm and determine whether the patient may be at risk of recurrence or early invasion, several potential molecular markers have been identified in the past [15].

Until recently, there were only few data on the prognostic role of HIF-1α in human cancer [2,7,13,16,17]. In the present study, HIF-1α expression was a common event in superficial bladder UC. Under normoxia, the proteasome pathway promotes the intracellular degradation of HIF-1α and thus its overexpression is a marker of hypoxia [4,8]. These data can explain why HIF-1α-positive

### TABLE 1 The incidence of HIF-1α expression, apoptosis, cell proliferation, p53 accumulation, VEGF expression and MVD for each histological grade and T-stage, and the correlation of HIF-1α expression with other variables

<table>
<thead>
<tr>
<th>Variable (n)</th>
<th>HIF-1α (high/low)</th>
<th>Mean (SEM)</th>
<th>Mean (SEM)</th>
<th>p53</th>
<th>Mean (SEM)</th>
<th>Mean (SEM)</th>
<th>Mean (SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I (30)</td>
<td>16/14</td>
<td>7.43 (1.05)</td>
<td>0.62 (0.14)</td>
<td>6/24</td>
<td>20/10</td>
<td>6.40 (1.65)</td>
<td>10.87 (1.41)</td>
</tr>
<tr>
<td>II (88)</td>
<td>38/50</td>
<td>11.43 (1.28)</td>
<td>0.93 (0.10)</td>
<td>42/46</td>
<td>56/32</td>
<td>10.86 (1.76)</td>
<td>15.32 (0.93)</td>
</tr>
<tr>
<td>III (22)</td>
<td>20/2</td>
<td>21.04 (5.53)</td>
<td>3.30 (0.68)</td>
<td>12/10</td>
<td>16/6</td>
<td>15.45 (4.10)</td>
<td>22.18 (1.17)</td>
</tr>
<tr>
<td>T-stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ta (42)</td>
<td>26/16</td>
<td>8.76 (0.85)</td>
<td>0.67 (0.05)</td>
<td>12/30</td>
<td>26/16</td>
<td>6.29 (1.64)</td>
<td>13.43 (1.46)</td>
</tr>
<tr>
<td>T1 (98)</td>
<td>48/50</td>
<td>13.50 (1.76)</td>
<td>1.47 (0.27)</td>
<td>48/50</td>
<td>66/32</td>
<td>12.49 (1.74)</td>
<td>16.31 (0.92)</td>
</tr>
<tr>
<td>P</td>
<td>0.17</td>
<td>0.07</td>
<td>0.02</td>
<td>0.048</td>
<td>0.33</td>
<td>0.03</td>
<td>0.064</td>
</tr>
<tr>
<td>Low (66)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High (74)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (140)</td>
<td>74/66</td>
<td>12.8 (1.28)</td>
<td>1.24 (0.17)</td>
<td>60/80</td>
<td>92/48</td>
<td>10.63 (1.35)</td>
<td>15.44 (0.79)</td>
</tr>
</tbody>
</table>

### TABLE 2 Univariate analysis (log-rank test) and the Cox’s proportional hazard estimation of the recurrence-free and progression-free survival in superficial UCs

<table>
<thead>
<tr>
<th>Variable</th>
<th>Survival</th>
<th>Recurrence-free</th>
<th>Progression-free</th>
</tr>
</thead>
<tbody>
<tr>
<td>Univariate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P for: Grade</td>
<td>0.040</td>
<td>0.512</td>
<td></td>
</tr>
<tr>
<td>T-stage</td>
<td>0.341</td>
<td>0.018</td>
<td></td>
</tr>
<tr>
<td>Ki-67 LI (&lt;8.6% vs &gt;8.6%)</td>
<td>0.029</td>
<td>0.398</td>
<td></td>
</tr>
<tr>
<td>AI (0.73% vs &gt;0.73%)</td>
<td>0.261</td>
<td>0.873</td>
<td></td>
</tr>
<tr>
<td>p53 expression (+ vs –)</td>
<td>0.038</td>
<td>0.047</td>
<td></td>
</tr>
<tr>
<td>bcl-2 expression (+ vs –)</td>
<td>0.031</td>
<td>0.652</td>
<td></td>
</tr>
<tr>
<td>VEGF-positive cells (&lt;5% vs &gt;5%)</td>
<td>0.036</td>
<td>0.044</td>
<td></td>
</tr>
<tr>
<td>MVD (&lt;15 vs &gt;15)</td>
<td>0.114</td>
<td>0.885</td>
<td></td>
</tr>
<tr>
<td>HIF-1α expression (low vs high)</td>
<td>0.284</td>
<td>0.058</td>
<td></td>
</tr>
<tr>
<td>HIF-1α/p53 (+/+ vs all other)</td>
<td>0.591</td>
<td>0.028</td>
<td></td>
</tr>
<tr>
<td>Cox</td>
<td>Grade</td>
<td>T-stage</td>
<td>P</td>
</tr>
<tr>
<td>Covariate coefficient (SEM)</td>
<td>0.586 (0.319)</td>
<td>1.452 (0.522)</td>
<td></td>
</tr>
<tr>
<td>Relative risk (95% CI)</td>
<td>1.797 (0.96–3.36)</td>
<td>4.27 (1.54–11.88)</td>
<td></td>
</tr>
<tr>
<td>Cox</td>
<td>Ki-67 index</td>
<td>HIF-1α/p53</td>
<td>P</td>
</tr>
<tr>
<td>Covariate coefficient (SEM)</td>
<td>0.852 (0.369)</td>
<td>0.970 (0.499)</td>
<td></td>
</tr>
<tr>
<td>Relative risk (95% CI)</td>
<td>2.35 (1.14–4.84)</td>
<td>2.64 (0.993–7.01)</td>
<td></td>
</tr>
</tbody>
</table>
cells were more prominent at tumour margins, away from capillaries and in the periphery of necrotic areas; the latter were more common in poorly differentiated UCs, explaining in part the association of HIF-1α accumulation with advanced grade. Although HIF-1α protein was expressed more in high-grade superficial UCs, there was significant inter-tumour variation, with the highest expression in some Ta tumours. This, combined with the most common diffuse pattern of HIF-1α staining, suggests that hypoxia alone may not be responsible for triggering the HIF-1α pathway. Moreover, the genetic alterations of various tumour-suppressor genes have been implicated in the up-regulation of HIF-1α [2,16].

Through activating the angiogenic pathways and modulating gene expression [4,5,7] HIF-1α leads to increased angiogenesis and triggers tumour growth, explaining the relationship of the hypoxic factor with proliferative activity. In the present study, HIF-1α expression also correlated well with the rate of apoptosis. Besides stimulating tumour growth, HIF-1α also acts by supporting apoptosis of neoplastic cells; this pro-apoptotic function is mainly a result of stabilizing wild-type p53, which induces apoptosis, and down-regulating the apoptosis inhibitor bcl-2 [7,13]. This might explain the association between HIF-1α expression and the AI. Another possibility is that enhanced apoptosis accompanies the HIF-1α-induced active cell proliferation, probably reflecting a cellular attempt at homeostatic autoregulation of tumour size, or as a result of the genetic instability of neoplastic cells and loss of normal mechanisms controlling cell death, leading to simultaneous increased cell proliferation and apoptotic cell death, as described previously [8,9]. This can also explain the increase in AI in poorly differentiated, highly proliferating tumours. There was also a strong correlation between HIF-1α expression and increased MVD. HIF-1α-induced activation of VEGF promotes neoangiogenesis, which is necessary for cellular adaptation to hypoxic stimuli and cancer cell proliferation [18].

Ki-67 nuclear antigen is a good immunohistochemical marker of proliferative activity in bladder cancer [19], having been correlated with the traditional prognostic factors of grade and stage in superficial UC [20], e.g. as in the present study. There was a correlation of proliferative rate with the time to recurrence; the Ki-67 LI remained an independent prognostic factor of tumour recurrence in the multivariate analysis. The positive correlation between the Ki-67 growth fraction and recurrence-free survival was reported previously [20,21], emphasising the possible role of the Ki-67 monoclonal antibody as a valuable indicator of superficial UCs at higher risk of recurrence.

High-grade and high-stage tumours were clearly more often positive for p53, which is in agreement with previous results [22]. This finding supports the biological role of mutant p53 as a marker of proliferative tendency and biological aggressiveness of UC. There was no association between the presence of bcl-2 expression and grade or stage, as noted previously [9]. Interestingly, bcl-2 positivity was linked to higher recurrence, but not with disease progression, which is consistent with the results of Lipponen et al. [23]. However, the issue of the prognostic significance of bcl-2 expression in superficial UCs is still controversial, as many studies have not established its value as a negative prognosticator [24], or others have even postulated a lesser probability of recurrence in Ta-T1 UCs in the presence of bcl-2 [9].

In the present study there was a direct relationship between VEGF and the classical biological indicators of grade and stage, indicating the importance of the switch to the VEGF angiogenic phenotype for tumour progression and dedifferentiation in superficial UC. However, the multivariate analysis showed no independent prognostic value for VEGF expression in patients with superficial bladder cancer.

The tendency of superficial UCs with poor differentiation and advanced stage to have a higher MVD has been reported before [12] and confirmed here, supporting an important role for neovascularity in superficial bladder cancer. However, MVD was neither predictive of tumour recurrence nor a marker of progression in the present series. Our data are consistent with increasing information showing no predictive value of the degree of vascularity for recurrence and progression of superficial UCs [12,25,26]. The results conflict with the study of Ozer et al. [27], who...
reported that angiogenesis was a predictor for the risk of recurrence in superficial UC; however, that study comprised patients with grade 3, stage T1 tumour, and microvessels were quantified by stereological methods. Moreover, Goddard et al. [28] reported that MVD at presentation is a significant predictive factor for subsequent muscle invasion in superficial bladder cancer. These differing and contrasting results possibly reflect the different methods of measuring MVD. Although a high MVD has been associated with a poor outcome in invasive bladder cancer [29], a similar association has not been reported satisfactorily for superficial disease. Moreover, the clinical importance of MVD has also recently been disputed in invasive UCs [30].

The major finding in the present study was the dismal prognostic influence of HIF-1α overexpression on disease progression in patients with superficial bladder UC. Although in the multivariate analysis HIF-1α was not of prognostic significance, its overexpression combined with the accumulation of mutant p53 nuclear protein indicates an aggressive phenotype, suggesting a potential biological model predictive of the future risk of disease progression. The presence of strong nuclear p53 staining reflects the increased expression of a nonfunctional p53 protein with a prolonged half-life that is detected by immunohistochemistry. Under these circumstances, HIF-1α can no longer support hypoxia-mediated apoptosis via stabilization of the wild-type p53 [13]. It therefore appears that the combination of HIF-1α overexpression and p53 protein dysfunction seems to be necessary to allow HIF-1α to stimulate cancer progression, through mediating angiogenesis and metabolic adaptation to O2 deprivation, without supporting p53-induced pro-apoptotic mechanisms [13].

That early invasive cancer is associated with a poor prognosis has prompted more aggressive treatment for high-risk superficial tumours. The development of uncontrolled cell growth which leads to an early invasive capability is a complex process with many and diverse pathways that are still poorly understood. Although none of the potential predictive molecules may serve as a single reliable tool for the early and accurate prediction of tumour recurrence and progression, it is becoming more apparent that no single marker, but rather a combination of different markers, will help to identify patients at risk of disease progression, and distinguish responsive from unresponsive superficial tumours [15]. Understanding the hypoxic molecular changes might provide an opportunity to expand traditional staging systems by creating molecular profiles that may more accurately characterize the biological potential of superficially confined bladder tumour. As with the other currently available molecular markers, the exact significance of hypoxic indicators remains to be addressed in large prospective, comparative and highly selective clinical studies.

CONFLICT OF INTEREST
None declared.

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Abbreviations: UC, urothelial carcinoma; HIF, hypoxia-inducible factor; VEGF, vascular endothelial growth factor; MVD, microvessel density; TUR, transurethral resection; AI, apoptotic index; Ki–67 LI, Ki–67 labelling index.
Interleukin–4 gene intron–3 polymorphism is associated with transitional cell carcinoma of the urinary bladder

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OBJECTIVE
To evaluate whether polymorphism of the interleukin-4 gene exon 3, and of the interleukin-1β gene exon 5 and promoter region, are associated with transitional cell carcinoma (TCC) of the urinary bladder, as cytokines are hypothesized to be important in cancer formation.

PATIENTS, SUBJECTS AND METHODS
The study included 138 patients with TCC of urinary bladder and 105 healthy controls living in the same area. Each genetic polymorphism was typed using polymerase chain reaction–based restriction analysis. Genotype distribution and allelic frequencies between patients and controls were compared.

RESULTS
There were significant differences in genotype and allelic distribution of intron 3 RP1/RP2 polymorphism (P < 0.001), but no significant difference in genotype distribution or allelic frequencies of the interleukin-1β gene polymorphism between patients with bladder cancer and controls.

CONCLUSION
The interleukin-4 gene intron 3 polymorphism is associated with bladder cancer and is a potential genetic marker in screening for the possible causes of bladder cancer.

KEYWORDS
interleukin-1 and –4, polymorphism, bladder cancer, transitional cell carcinoma

INTRODUCTION
In Taiwan, urinary bladder cancer is one of the most common urological malignancies and most such tumours are TCC; it is a complex and multifactorial disease. Risk factors associated with bladder cancer include cigarette smoking, chemical exposure, and an unknown exposure risk factor of endemic black-foot disease in southern Taiwan [1]. Genetic factors may have a role in the formation of bladder cancer. Some genetic polymorphisms are associated with bladder cancer, e.g. of p53 and p21 [2,3].

Cytokines are signalling molecules contributing to the inflammatory response, and protect the body from pathogens and other environmental factors. Cytokines comprise several proteins that are key components in the pathogenesis of many diseases, including cancer. Interleukin–1β, located at chromosome 2q12, is a potent pro-inflammatory agent which is central in immunoregulation, fever, inflammation and cancer formation [4]. Polymorphisms of the interleukin–1β gene promoter region and exon 5 have been screened for their role in the occurrence and severity of rheumatoid arthritis and osteoporosis [4,5].

Interleukin–4 is a key cytokine that induces the activation and differentiation of B cells, and the development of the Th2 subset of lymphocytes. Th2 cytokines such as interleukin–4, -6 and -10 primarily support antibody production, and many studies have confirmed that patients with cancer have high levels of such cytokines in their serum [6–8]. Interleukin–4 also inhibits macrophage activation and might be involved in cancer formation. The interleukin–4 gene has been mapped to the q arm (q23–31) of chromosome 5 [9], and is in a cluster of cytokine genes (interleukin–3, -5, -9, -13 and -15, granulocyte colony-stimulating factor, and interferon regulatory factor) [10]. A polymorphism of the interleukin–4 gene is located in the third intron, and is composed of a 70-bp sequence of variable numbers of tandem repeats (VNTR) [11].

In the present study we assessed the interleukin–1β and interleukin–4 genes because they have been reported to be associated with several different cancers [12,13]. To elucidate whether these polymorphisms are important in the susceptibility to bladder cancer, we investigated and compared the distribution of these polymorphisms between a control group and patients with bladder cancer, by analysing the results of PCR.

PATIENTS, SUBJECTS AND METHODS
The study comprised 138 patients from central Taiwan (109 men and 42 women, mean age 65.9 years, SD 12.2, range 42–80) with bladder cancer, treated in the authors’ institution, from April 1998 to December 2001. All of the pathological cell types in the cancer group were TCC. Patients were subdivided into those with invasive and noninvasive cancer, according to their pathological grading and clinical course. The patients with noninvasive and invasive cancer were classified as having pathologically superficial (Ta and T1) and invasive (T2a and T2b) tumours, using the American Joint Committee on Cancer staging system; there were 76 patients with noninvasive and 62 with invasive disease. From pathological grading, 36 patients were grade I, 68 grade II and 34 grade III.
The control group comprised 105 healthy volunteers (65 men and 40 women, mean age 53.5 years, SD 10.3, range 40–87) from the same area; none had a history of cancer. Routine urinary tests were used to exclude any control subjects who may have had microscopic haematuria. Informed consent was obtained from all patients and subjects participating in the study. Genomic DNA was prepared from peripheral blood using the Genomaker DNA Extractor kit (Blooms, Taiwan).

The total PCR volume was 25 μL and was composed of 2.5–10 pmol of each primer, 10 mmol/L Tris–HCl (pH 8.3), 50 mmol/L KC1, 2.0 mmol/L MgCl2, 0.2 mmol/L of each deoxyribonucleotide triphosphate, and 1 unit of AmpliTaq DNA polymerase (Perkin Elmer, Forster City, CA, USA).

Primers for the interleukin-4 gene intron 3 polymorphism were: upstream 5'-AGGCTGAAAGGGGGAAAGC-3', and downstream 5'-CTGTTCACCTCAACTGCTCC-3' [11,14]. The cycling conditions were 95°C for 30 min, 55°C for 30 min and 72°C for 30 min. The interleukin-4 gene intron 3 polymorphism PCR products, including the 70-bp VNTR region, were directly analysed by 3% agarose gel electrophoresis, and each allele recognized according to its size. The RP1 and RP2 alleles were 183 bp and 253 bp, respectively.

The primers for the interleukin-1β gene promoter region –511/CT polymorphism were: upstream 5'-TGCCATTGATCTGGTTCATC-3', and downstream 5'-GTTAAGAATCTGGACCCAAGA-3' [4]. The cycling conditions were as given above. The restriction enzyme for the analysis was Ava I (New England Biolabs, Beverly, USA); 304 bp of PCR product was digested into 190 bp + 114 bp if the restriction site was present (‘C’ allele). This polymorphism was detected by restriction analysis based on the report by Cantagrel et al. [4].

Primers for the interleukin-1β gene exon 5 polymorphism were: upstream 5'-GTTGTCATGACACTTGGACC-3', and downstream 5'-CTCAGATCCATGAGGACCCAAGA-3'. The cycling conditions were as given above. The region containing the polymorphic site within exon 5 of the interleukin-1β gene was amplified and then digested by Taq I (New England Biolabs). Class ‘E1’ was 135 bp + 114 bp and ‘E2’ was 249 bp, as shown on electrophoresis. For quality control, part of the samples were sequenced to confirm the results. Before sequencing, PCR fragments were purified from the agarose gel using QIAEX II kit (Qiagen, Germany). Direct sequencing used a d-rodamine DyeDeoxy Terminator Sequencing kit (PE Applied Biosystems, Foster City, CA) with an ABI Prism 377 DNA Sequencer (PE Applied Biosystems).

The allelic frequency and genotype distributions of these polymorphisms in both groups were analysed using the chi-square test. When the assumption of the chi-square test was violated (i.e. when one cell had an expected count of <1, or >20% of the cells had an expected count of <5), Fisher’s exact test was used; in both P < 0.05 was to indicate statistical significance. Odds ratios (OR) were calculated from allelic frequencies and carriage rates, with 95% CI.

### RESULTS

The genotype distributions and allelic frequencies of the intron 3 regions in the interleukin-4 gene obtained from patients and controls are shown in Table 1; there were significant differences in genotype distribution of this polymorphism between the groups (P < 0.001), with significantly more patients with the RP1 homozygote (86%) than controls (64%). The OR (95% CI) for the RP1 homozygote and heterozygote was 8.88 (1.02–77.16) [P = 0.018] and 2.73 (0.289–25.73) [P = 0.359], respectively. The patients were further categorized into three groups according to pathological grading, but there were no significant differences in this polymorphism among the groups (Table 2). There was a significant difference in the genotype distribution of interleukin-4 intron 3 RP1/RP2 polymorphism between the noninvasive and invasive group (P = 0.002, Fisher’s exact test); the distribution of RP1 in the invasive was significantly higher than that in the noninvasive group.

The genotype frequencies of the promoter and exon 5 regions of the interleukin-1β gene in the two groups are also shown in Table 1. There were neither significant differences in the genotype distributions nor allelic frequencies of the interleukin-1β gene promoter and exon 5 polymorphism between the patients and controls.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Controls</th>
<th>P</th>
<th>Cancer</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interleukin-4 gene intron 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>105</td>
<td>138</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genotype</td>
<td>RP1/RP1</td>
<td>67 (64)</td>
<td>119 (86)</td>
<td></td>
</tr>
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<td></td>
<td>RP1/RP2</td>
<td>33 (31)</td>
<td>18 (13)</td>
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</tr>
<tr>
<td></td>
<td>RP2/RP2</td>
<td>5 (5)</td>
<td>1 (1)</td>
<td></td>
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<tr>
<td>Allelic frequencies</td>
<td>RP1</td>
<td>167 (80)</td>
<td>256 (93)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RP2</td>
<td>43 (21)</td>
<td>20 (7)</td>
<td></td>
</tr>
<tr>
<td>Interleukin-1 promotor</td>
<td>N</td>
<td>105</td>
<td>130</td>
<td></td>
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<tr>
<td>Genotype</td>
<td>C/C</td>
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<td>25 (20)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C/T</td>
<td>50 (48)</td>
<td>74 (60)</td>
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<td>T/T</td>
<td>27 (26)</td>
<td>24 (20)</td>
<td></td>
</tr>
<tr>
<td>Allelic frequencies</td>
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<td>106 (51)</td>
<td>124 (50)</td>
<td></td>
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<tr>
<td></td>
<td>T</td>
<td>104 (49)</td>
<td>122 (49)</td>
<td></td>
</tr>
<tr>
<td>Interleukin-1 exon 5</td>
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<td></td>
<td></td>
<td></td>
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<td>102 (97)</td>
<td>127 (98)</td>
<td></td>
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<td>E1/E2</td>
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<td></td>
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<tr>
<td></td>
<td>E2/E2</td>
<td>0</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Allelic frequencies</td>
<td>E1</td>
<td>207 (98.6)</td>
<td>256 (98.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>E2</td>
<td>3 (1.4)</td>
<td>4 (1.5)</td>
<td></td>
</tr>
</tbody>
</table>

**TABLE 1** Comparison of the genotype distributions and allelic frequencies for interleukin-4 gene intron 3 region, and interleukin-1β gene promoter and exon 5, in patients with bladder cancer or in healthy control subjects.
DISCUSSION

The interleukin-4 gene intron 3 polymorphism showed significantly different distributions between normal controls and patients with cancer, but there was no association between the interleukin-1 gene and bladder cancer, indicating that this gene and its inflammatory response is less likely to be associated with bladder cancer. The association between bladder cancer and various genetic markers has helped to increase knowledge of the genetics of the immune response to and pathogenesis of bladder cancer.

In the present analysis, we chose to screen polymorphisms in the interleukin-4 gene; the RP1/RP2 polymorphism in intron 3 may enhance cancer formation either through an IgE pathway, or its transcription activity. The function of the RP1/RP2 intron 3 polymorphism is unknown; possibly distinct numbers of VNTR copies might affect the transcriptional activity of the interleukin-4 gene. Why the RP1/RP2 intron 3 polymorphism of this gene is associated with bladder cancer and tumor invasiveness should be further clarified; future studies could lead to immunotherapy for bladder cancer. However, the relationship between bladder cancer and interleukin-4 gene polymorphism has been studied less; to our knowledge, the present is the first study of the association of interleukin-4 gene intron 3 RP1/RP2 polymorphism with bladder cancer. The relationship between cytokines and the severity of bladder cancer is worth further investigation.

Seddighzadeh et al. [15] studied 164 bladder tumours and found a large variation in mRNA levels of interleukin-1α; the association of interleukin-1α expression and cancer-specific survival was not statistically significant. The evidence for a mechanism of tumour growth inhibition by interleukin-1α is weak. Kuo et al. [16] also found no statistical significance of interleukin-1α and −1β activities in blood cultures from patients with bladder cancer when compared with control subjects; the present data are compatible with their findings.

In the present study, that interleukin-1 was not significantly associated with bladder cancer formation may have been because there was an incomplete match between the serum level and its expression in tissue, or because interleukin-1 influenced tumour progression but not formation. This problem provides a target for further studies.

In conclusion, the interleukin-4 gene intron 3 polymorphism is associated with bladder cancer but the mechanism remains unclear. However, the interleukin-4 but not interleukin-1 gene might be a potential genetic marker in screening for the possible causes of bladder cancer.

ACKNOWLEDGEMENTS

This study was supported by a grant from the China Medical University Hospital (DMR-90–043).

CONFLICT OF INTEREST

None declared.

REFERENCES


**TABLE 2** Distribution of interleukin-4 gene polymorphism genotypes in patients with bladder cancer according to pathological grading and clinical staging

<table>
<thead>
<tr>
<th>Group</th>
<th>RP1/RP1</th>
<th>RP1/RP2</th>
<th>RP2/RP2</th>
<th>Total</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>27 (75)</td>
<td>9 (25)</td>
<td>0</td>
<td>36</td>
<td>0.69</td>
</tr>
<tr>
<td>II</td>
<td>62 (91)</td>
<td>5 (7)</td>
<td>1 (1.4)</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>30 (88)</td>
<td>4 (12)</td>
<td>0</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>119</td>
<td>18</td>
<td>1</td>
<td>138</td>
<td></td>
</tr>
<tr>
<td>Invasiveness</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.002*</td>
</tr>
<tr>
<td>Non-invasive</td>
<td>60 (79)</td>
<td>16 (21)</td>
<td>0 (0)</td>
<td>76</td>
<td></td>
</tr>
<tr>
<td>Invasive</td>
<td>59 (95)</td>
<td>2 (3)</td>
<td>1 (1.6)</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>119</td>
<td>18</td>
<td>1</td>
<td>138</td>
<td></td>
</tr>
</tbody>
</table>

*Fisher’s exact test.

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Abbreviations: VNTR, variable numbers of tandem repeats.
**In vivo** accumulation of different hypericin ion pairs in the urothelium of the rat bladder

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**OBJECTIVE**

To optimise the diagnostic and phototherapeutic efficacy of hypericin in superficial bladder cancer, by developing a bladder instillation fluid that does not depend on the presence of plasma proteins for an appropriate and reliable urothelial uptake of hypericin.

**MATERIALS AND METHODS**

Sodium hypericinate (in distilled water, in sodium phosphate buffer, or in polyethylene glycol) and several other hypericinate salts (potassium, lysine, TRIS or hexylamine) were instilled with no plasma constituents into the rat bladder. The accumulation of hypericin was assessed with fluorescence microscopy.

**RESULTS**

The diagnostic and phototherapeutic efficacy of hypericin depends on its ability to penetrate the tumour lesions sufficiently to show a fluorescent signal or elicit a photodynamic response. Several instillation fluids meet the purpose, as the urothelial accumulation of hypericin was similar to that obtained with the instillation fluid supplemented with plasma proteins, used in clinical practice. The highest concentrations of hypericin in the urothelium of the rat bladder were obtained with hypericin instillation solutions prepared with distilled water or 20% polyethylene glycol 400 in distilled water. Fluorescence microscopy showed that hypericin was selectively localized in the urothelium. Furthermore, all variables investigated (hydrophilic/lipophilic balance, pH, saline, presence of organic solvent) can dramatically influence the *in vivo* accumulation of hypericin.

**CONCLUSION**

An appropriate and reliable urothelial uptake of hypericin does not depend on the presence of plasma protein supplements in the bladder instillation fluid.

**KEYWORDS**

hypericin, ion pairs, accumulation, bladder, photodynamic therapy

**INTRODUCTION**

Hypericin is a hydroxylated phenanthroperylenequinone present in several plants of the widely distributed genus *Hypericum*, the most common of which is *H. perforatum* [1,2]. Besides showing a high fluorescence quantum yield [3,4], it can generate singlet oxygen efficiently [4,5]. Interestingly, when instilled in human bladders, hypericin localizes specifically in papillary and flat transitional carcinoma cells *in situ*. Consequently, the compound is currently used as a clinical diagnostic tool for detecting early-stage urothelial carcinoma of the bladder [6–9]. As hypericin is a potent photosensitizer, its specific localization offers a unique opportunity not only to detect but also to treat the lesions photodynamically [10–14].

Before its use as a bladder diagnostic, hypericin is solubilized in an instillation fluid containing a stabilized solution of hypericin.

Plasma proteins (Red Cross, Belgium) [6,7] to which hypericin adsorbs [15]. The amount of (lipid)proteins critically determines the cellular accumulation of hypericin [12,15], and as the plasma protein preparation is not widely available, the composition of the instillation fluid makes a more widespread application of the diagnostic method difficult. To optimise the clinical application, an appropriate instillation fluid without plasma constituents is therefore important.

Deprotonation of hypericin is possible at the phenolic bay- and peri- groups, with pK values of 1.7 and 12.5, respectively [16–18]. The stability of the bay anion and the ease of ionization are a result of the proximity of the hydroxyl groups that allows one hydrogen to be shared between oxygen atoms, thus forming hydrogen bonds [Fig. 1]. Therefore, at physiological pH hypericin is negatively charged and forms organic and inorganic monobasic salts [19]. Unexpectedly, these salts are practically insoluble in water, and in all respects behave as closely associated lipophilic ion pairs. Different salts (ion pairs) of hypericin vary in their physicochemical properties, including solubility in organic solvents and formation of a dispersion in water. For instance, lysine hypericinate is much more soluble in water than sodium hypericinate [20]. Therefore, ion-pair formation is a unique feature of hypericin that allows the straightforward preparation of hypericins with a variable lipophilic/hydrophilic balance, avoiding the need for complex chemical synthetic work.

The diagnostic and phototherapeutic efficacy of hypericin in superficial bladder cancer depends on its ability, after instillation, to penetrate the tumour lesions enough to give a fluorescent signal or elicit a photodynamic response. The present study was aimed at developing a bladder instillation fluid that does not depend on the presence of plasma proteins for an appropriate and reliable urothelial uptake of hypericin. Furthermore,
Hypericin was synthesized from emodin anthraquinone according to Falk and Oberreiter [21]. Briefly, emodin (2.5 g), isolated from the cortex of Frangula, was dissolved in 125 mL acetic acid and reduced with 5 g SnCl2·2H2O in 65 mL concentrated HCl. After refluxing the mixture for 3 h at 120 °C, emodin anthrone was precipitated by cooling to room temperature. To prepare protohypericin via oxidative dimerization, 2 g emodin anthrone was dissolved in 44 mL pyridine-1-oxide and 100 mg of FeSO4·7H2O added. The reaction mixture was heated at 80 °C for 1 h under nitrogen in the dark. The PC of hypericin in the different instillation fluids (30 μmol/L) were prepared in: (a) distilled water (HyH2O); (b) polyethylene glycol (PEG) 400 (20%) in distilled water (HyPEG20); (c) PEG 400 (HyPEG); (d) PBS pH 7.4, including 150 mmol/L NaCl and other constituents (Gibco-BRL, Paisley, Scotland) (HyPBS pH 7.4); (e) sodium phosphate buffer (10 mmol/L NaH2PO4) pH 4, 7 and 10 (HyNa pH 4, 7, 10); (f) potassium phosphate buffer (10 mmol/L K2HPO4) pH 7 (HyKpH7); (g) lysine in distilled water (10 mmol/L lysine) pH 7 (HyLys pH 7); and (i) hexylamine in distilled water (10 mmol/L hexylamine) pH 7 (HyHA pH 7). In addition, a hypericin solution in a 1% SOPP (SOPP; Red Cross, Brussels, Belgium; HySOPP) was prepared; this solution is presently used as the bladder instillation fluid for the fluorescent diagnosis of bladder tumours in the clinic [6,7]. HySOPP was prepared by dissolving 5 mg of hypericin in 1 mL NaOH (0.1 mol/L) and 2 mL PEG 400, followed by neutralization with 1 mL acetic acid (0.1 mol/L). The mixture was then diluted with 33 mL of 4% SOPP and kept in the dark at room temperature for 30 min. After sterilization by membrane filtration, the solution was further diluted with PBS to obtain a 75 μmol/L hypericin solution in 1% SOPP. This solution was kept at −20 °C in the dark and thawed and diluted in normal saline before use.

PREPARATION OF HYPERICIN ION PAIRS

Different hypericin instillation fluids (30 μmol/L) were prepared in: (a) distilled water (HyH2O); (b) polyethylene glycol (PEG) 400 (20%) in distilled water (HyPEG20); (c) PEG 400 (HyPEG); (d) PBS pH 7.4, including 150 mmol/L NaCl and other constituents (Gibco-BRL, Paisley, Scotland) (HyPBS pH 7.4); (e) sodium phosphate buffer (10 mmol/L NaH2PO4) pH 4, 7 and 10 (HyNa pH 4, 7, 10); (f) potassium phosphate buffer (10 mmol/L K2HPO4) pH 7 (HyKpH7); (g) lysine in distilled water (10 mmol/L lysine) pH 7 (HyLys pH 7); and (i) hexylamine in distilled water (10 mmol/L hexylamine) pH 7 (HyHA pH 7). In addition, a hypericin solution in a stabilized solution of human plasma proteins (SOPP; Red Cross, Brussels, Belgium; HySOPP) was prepared; this solution is presently used as the bladder instillation fluid for the fluorescent diagnosis of bladder tumours in the clinic [6,7]. HySOPP was prepared by dissolving 5 mg of hypericin in 1 mL NaOH (0.1 mol/L) and 2 mL PEG 400, followed by neutralization with 1 mL acetic acid (0.1 mol/L). The mixture was then diluted with 33 mL of 4% SOPP and kept in the dark at room temperature for 30 min. After sterilization by membrane filtration, the solution was further diluted with PBS to obtain a 75 μmol/L hypericin solution in 1% SOPP. This solution was kept at −20 °C in the dark and thawed and diluted in normal saline before use.

DETERMINATION OF THE PARTITION COEFFICIENT, PC

The PC of hypericin in the different instillation fluids and octanol were determined. The hydrophilic phase (instillation fluid) and the lipophilic phase were pre-saturated with each other, followed by diluting the hypericin stock solution (30 mmol/L) of hypericin in DMSO at 1000-fold in a 50:50 mixture (1 mL) to give a final hypericin concentration of 30 μmol/L. The samples were vortexed at high speed for 2 min and placed in a shaker for 30 min; they were then centrifuged for 5 min at 5000 g to separate the octanol from the hydrophilic phase. The latter was removed, concentrated under reduced pressure and the residue taken up in an equal volume of octanol. The hypericin content in each phase was determined using a microplate fluorescence reader (FL 600 Bio-tek, Winooski, VT, USA) with excitation and emission filters of 580/20 nm and 645/40 nm, respectively. The concentration of hypericin in each phase, as determined from the calibration curve, was determined. The concentrations were then used to calculate log PCoctanol/instillation fluid.

INTRAVESICAL INSTILLATION OF HYPERICIN PREPARATIONS IN THE RAT BLADDERS

Female Fischer rats (CDF®, F-344) weighing 150–175 g were purchased from Charles River Laboratories (Lyon, France); they were provided with chow and water ad libitum. All animal procedures were in compliance with national and European regulations and, were approved by the Animal Care and Use Committee of KU Leuven. To study the accumulation of hypericin in the normal bladder, rats were anaesthetized (pentobarbital, intraperitoneal 45 mg/kg) and after catheterization, 0.5 mL of the different freshly prepared hypericin instillation fluids (30 μmol/L) instilled into the rat bladders for 2 h before evaluating the biodistribution, as described previously [14].

Fluorescence microscopy with image analysis was used to assess and quantify the fluorescence in sections of bladder tissue. At the end of hypericin instillation, the fluids were withdrawn, the bladders rinsed through the catheter with normal saline and the rats killed. Bladders were then removed, cut open, immediately transferred into Tissue Tek embedding medium (Miles, Elkhart, IN, USA) and immersed in liquid nitrogen. Two consecutive 5-μm sections were cut on a cryostat. The first section was stained with haematoxylin and eosin, and the second examined by fluorescence microscopy (Axioskop 2 Plus, Carl Zeiss, Göttingen, Germany) using a 535/25 nm band-pass.
excitation filter and a 590 nm long-pass emission filter. Fluorescence images were taken using a light-sensitive charge-coupled device digital camera (AxioCam HR, Carl Zeiss). Rapid processing avoided significant photobleaching of the hypericin-induced fluorescence in the cells. For uniformity, all parameters pertaining to fluorescence excitation and detection were held constant throughout the study. An imaging software system (Carl Zeiss, Vision, Hallbergmoos, Germany) was used to measure the average fluorescence in consecutive layers of 1.5-μm thickness from the urothelium, through the submucosa to the muscle [22]. Fluorescence intensities were determined as the mean of eight measurements. Corrections were made for autofluorescence levels of the respective tissue layers, as measured using specimens from control animals. The relative fluorescence of hypericin from the apical layer (Fmax) to the inner layer (Fmin) of the bladder urothelium was calculated and the FD50 values (corresponding to the distance bladder urothelium was calculated and the FD50 values (corresponding to the distance the bladder tissue (Table 1 and Fig. 3) was given to determine the distance at which the photosensitizer fluorescence declines to half its maximum value) were calculated.

One-way ANOVA with the Tukey-Kramer post-hoc test was used to determine the significance of differences between means, with significance accepted at \( P < 0.05 \).

**RESULTS**

Table 1 shows the PCs determined by adding hypericin to an equal volume of octanol and the different instillation fluids. The three different groups had significantly different log PC values. While HyH2O, HyNa pH 7, HyNa pH 10, HyK pH 7 and HyLys pH 7 had low log PC values of 0.48–0.95, HyTRIS pH 7 and HyNa pH 4 had significantly higher values, of 1.45 and 1.84, respectively. HyHA pH 10 and HyPBS pH 7.4 had the highest penetration of hypericin into the lipophilic phase, with log PC values of 2.66 and 3.00, respectively. The log PC value for HyPEG, HyPEG20 and HySOPP preparations could not be determined because PEG is miscible with octanol, while for SOPP the proteins present (to which hypericin binds) precipitated.

To assess the influence of the different vehicles on the extent of hypericin accumulation into the normal bladder wall, the frozen bladder sections were assessed using fluorescence microscopy (Fig. 2).

**TABLE 1**

<table>
<thead>
<tr>
<th>Instillation fluid</th>
<th>Log PC</th>
<th>Fmax (f.u.)</th>
<th>Fmin (f.u.)</th>
<th>FD50</th>
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</thead>
<tbody>
<tr>
<td>HyH2O 0.61</td>
<td>245</td>
<td>29.2</td>
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<td>HyPEG 0.51</td>
<td>214</td>
<td>26.7</td>
<td>5.09</td>
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</tr>
<tr>
<td>HyPEG 0.50</td>
<td>5.04</td>
<td>0.43</td>
<td>3.12</td>
<td></td>
</tr>
<tr>
<td>HyPEG 3.00</td>
<td>69.1</td>
<td>1.11</td>
<td>5.40</td>
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<tr>
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<td>172</td>
<td>1.34</td>
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<tr>
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<td>103</td>
<td>0.85</td>
<td>3.54</td>
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<tr>
<td>HyK pH 7 0.89</td>
<td>92.4</td>
<td>2.97</td>
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<tr>
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<td>2.34</td>
<td>3.56</td>
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</tr>
<tr>
<td>HySOPP nd</td>
<td>81.2</td>
<td>3.14</td>
<td>3.74</td>
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**FIG. 2**. Fluorescence photomicrographs of sections of normal rat bladder instilled for 2 h with a freshly prepared hypericin (30 μmol/L) instillation fluid (×400). The instillation fluids were prepared using water (A), 20% PEG in water (B), PEG (C), PBS pH 7.4 (D), sodium phosphate pH 4 (E), sodium phosphate pH 7 (F), sodium phosphate pH 10 (G), potassium phosphate pH 7 (H), lysine pH 7 (I), TRIS pH 7 (J), hexylamine pH 7 (K) and SOPP (L). Scale bar = 50 μm.

Incubation with HyLys pH 7 resulted in bleeding, indicating urotheelial damage. The imaging software system used to measure the mean fluorescence in 1.5-μm thick layers of the bladder tissue (Table 1 and Fig. 3) gave \( F_{\text{max}} \) and \( F_{\text{min}} \) values. Incubation with HyH2O and HyPEG20 resulted in an overall greater fluorescence through the urothelium than did HySOPP. For example, the fluorescence in the apical layer of the urothelium was 3.0 and 2.6 times higher with HyH2O and HyPEG20, whereas \( F_{\text{max}} \) was 9.3 and 8.5 times higher, respectively, than with HySOPP. Incubation with HyNa pH 4 doubled the fluorescence in the first layer of the urothelium, while the fluorescence in the inner layer of the urothelium was 2.3 times lower than with HySOPP. HyPEG gave almost no fluorescence in the bladder tissue; fluorescence levels in the outer and inner layer of the urothelium were 16.1 and 7.3 times lower than with HySOPP. Only HyH2O and HyPBS significantly increased the relative penetration of hypericin, with \( F_{\text{D50}} \) values = 1.5 times higher than with HySOPP. The fluorescence was restricted to the urothelium (70–75 μm thickness), and the submucosa and muscle layers were virtually devoid of fluorescence (Fig. 3). Except for HyH2O, HyHA and HyPBS, instillation fluids with a higher log PC were...
FIG. 3. 
Quantification of hypericin fluorescence in layers of 1.5 μm thick in the normal rat bladder.
The results show hypericin fluorescence levels in normal rat bladder from the apical layer of
the urothelium towards the muscle after 2 h instillation with freshly-made hypericin (30 μmol/L)
instillation fluid. Each value represents the mean of at least eight measurements (coefficient of
variation <5%).

FIG. 4. The maximum fluorescence at the apical layer of the urothelium of the rat bladder, after 2 h
incubation with 30 μmol/L hypericin instillation fluids, as a function of the log PC. The correlation
\( R^2 = 0.9235 \) between \( F_{\max} \) and log PC for HyNa pH 4, HyNa pH 7, HyNa pH 10, HyK, HyLys and HyTRIS are
indicated by an unbroken line. The correlation
\( R^2 = 0.9999 \) between \( F_{\max} \) and log PC for HyH2O, HyHA and HyPBS is indicated with a dotted line.

more concentrated in the apical layer than those with a lower PC (Fig. 4). In these cases,
linear regression showed a strong correlation \( R^2 = 0.9336 \) between the fluorescence at the
apical layer of the urothelium and log PC. For HyH2O, HyHA and HyPBS, there was also a
strong correlation \( R^2 = 0.9999 \), but here the \( F_{\max} \) decreased with increasing log PC values.

DISCUSSION

Using specific instillation conditions that excluded the presence of plasma proteins,
blood instillation fluids were assessed for an appropriate transfer of hypericin to the
surrounding bladder urothelium. The uptake was investigated using rat bladders with
normal urothelium, as previous experiments have shown that, at least in this model, the
accumulation of hypericin is similar in normal urothelium and urothelial tumours [22]. As
the urothelial accumulation of hypericin was similar to that obtained with the instillation
fluid supplemented with plasma proteins used in clinical practice, the results show that
several instillation fluids (e.g. HyNa pH 7, HyPBS) meet the goal. Some instillation
conditions induced a substantially higher, and some a poorer, penetration of hypericin in the
urothelial layer.

As can be deduced from the partitioning experiments, ion-pair formation of hypericin
in similar ionic strength conditions with several cations allowed the straightforward
preparation of hypericins with variable lipophilicity. For instance, in accordance with
previous results showing that lysine hypericinate was much more soluble in water
than sodium hypericinate [20], the former had a higher affinity for the water phase than the
sodium ion pair, while in the presence of the hexylamine comprising a lipophilic alkyl
chain, hypericin concentrated particularly in the octanol phase. Moreover, the ionic
strength of the buffer in which hypericin is
'partitioning and

The permeability of a compound into tissue is mainly determined by its PC, while the
molecular weight and the possibility of hydrogen-bond formation are less important
[23–25]. Hence it was expected that conditions in which hypericin showed high
log PC values would lead to high penetration into the urothelial layer. Although most data
appear to support this principle, there was conflicting behaviour, especially for HyPBS
pH 7.4, HyHA pH 7 and HyH2O. Therefore no simple conclusions can be drawn about the
correlation of the urothelial penetration of the hypericin ion pairs and their log PC values.

The bladder surface is coated by a glycocalyx, which is synthesized by the fully
differentiated umbrella cells and is composed of a dense layer of glycosaminoglycans
(GAGs), most commonly present as constituents of proteoglycans, and glycoproteins or mucin. The high charge of
the GAGs and their high density on the urothelial surface causes a strict ordering of
water molecules, forming a very hydrophilic surface that cannot be penetrated by most
low molecular-weight solutes [26,27] and is correlated with the tightness of the bladder
wall. By forcing counter ions, ionic strengths and pHs on the bladder wall, it can be
expected that the different buffers instilled in the bladder impinge on the characteristics of
the GAG layer, modifying its penetrability for organic compounds. Unfortunately, this GAG
layer as a penetration-modifying factor cannot be reproduced in a simple water/ 

For HyPEG there was no hypericin penetration
in the bladder urothelium, confirming our
previous report that the compound
completely dissolves in this vehicle does not
penetrate into tissues [28], and subsequently
does not induce a photodynamic response
[29]. Although a dissolved drug is generally
more likely to diffuse from the vehicle into
biological membranes, the PC of a drug
between the membrane and the vehicle
generally decreases as the solubility in the
vehicle increases [30]. This is normally the
case when excessive solubilization of the
penetant in the vehicle results in a high
affinity between the vehicle and the
penetrant, thereby postponing its permeation
from the vehicle into the tissue. This hypothesis is supported by the observation that a five-fold dilution of PEG in water, a vehicle with a dramatically decreased solubility of hypericin, resulted in urothelial accumulation which was close to that when hypericin was dispersed in distilled water.

In conclusion, an appropriate and reliable urothelial uptake of hypericin does not depend on the presence of plasma proteins in the bladder instillation fluid. After instillation in human bladders for whole-bladder wall photodynamic therapy, these formulations are likely to induce photo-active concentrations of hypericin in bladder tumours. All variables investigated (hydrophilic/lipophilic balance, pH, saline, presence of organic solvent) influence the in vivo accumulation of hypericin. Some instillation conditions induced a much higher accumulation than with instillation fluid supplemented with plasma proteins used in clinical practice. Of interest, PEG 400 is a suitable vehicle for the storage and heat sterilization of high concentrations of hypericin, and by simple dilution in distilled water an instillation fluid could be prepared that is ready for diagnostic use. To what extent the hypericin instillation conditions with no plasma proteins maintain the high sensitivity and specificity for detecting superficial TCC tumours in humans will be investigated in the near future.

ACKNOWLEDGEMENTS

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CONFLICT OF INTEREST

None declared. Source of funding: Grants from FWO, Onderzoeksfonds and GOA.

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**Abbreviations:** DMSO, dimethylsulphoxide; GAG, glycosaminoglycan; PC, partition coefficient; PEG, polyethylene glycol; SOPP, stabilized solution of human plasma proteins.
An evaluation of laparoscopic tissue harvesting for human adult urological smooth muscle physiological experimentation

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OBJECTIVE
To evaluate the properties of laparoscopically harvested bladder neck and ureteric smooth muscle, compared with tissue obtained at open surgery.

MATERIALS AND METHODS
Bladder neck was harvested from patients undergoing open (eight) or laparoscopic radical prostatectomy (11). Ureter was obtained from patients undergoing nephrectomy (laparoscopic or open) and cystectomy (open only); obtained openly from 16 and laparoscopically from seven. Muscle strips dissected from these samples were perfused in a Brading-Sibley organ bath, and stimulated using standard agonists (100 μmol/L carbachol for bladder neck, 100 mmol/L KCl-enriched Krebs’ solution for ureteric muscle). Tensions produced were recorded using strain gauges and analysed using data-acquisition software. Results were compared by a two-tailed Fisher’s exact test to determine significance.

RESULTS
Openly harvested bladder neck muscle strips from six patients showed a measurable response to the standard agonist. Laparoscopically harvested bladder neck strips from only two patients showed any measurable response. Openly harvested ureteric muscle strips from 12 patients responded to K-enriched solution, while one patient’s laparoscopically harvested strips responded to stimulation. This difference was significant in both tissue groups separately (P < 0.025). Histological evaluation identified no specific differences between openly and laparoscopically harvested tissue.

CONCLUSION
The yield of smooth muscle available for research is significantly less when the resection is laparoscopic; this might be a result of diathermy damage at a subcellular level. With the increasing use of the laparoscopic approach in urological surgery, the effect on tissue availability for human smooth muscle physiological study is important to researchers in this field.

KEYWORDS
physiology, laparoscopy, research, ureter, bladder neck.

INTRODUCTION
Obtaining human urological tissue for experimentation is not always straightforward, and several techniques have been used. Historically, investigators have used relatively large muscle strips obtained at open operations [1–4]. The increasing use of the endoscopic approach to surgery has reduced the availability of open sampling. To circumvent this, many animal tissues have been described [5–9]. The use of these leads to questions about applicability to humans, as interspecies variation of physiology and pharmacology in detrusor smooth muscle is known to exist [5,10]. Other investigators have resorted to cadaveric tissue [11–13], accepting concerns about warm ischaemia time from the patient’s death to tissue harvest. To avoid these difficulties, others have harvested fresh human tissue endoscopically, using cold-cup biopsy forceps [14–16]. This method provides very small samples, which are difficult to manipulate and orientate, and may have been traumatized during harvesting. Also, there are concerns about the risk of perforation of the structure being biopsied, effectively limiting their use to detrusor muscle. Finally, there are ethical concerns about the biopsy of tissue from healthy patients who derive no benefit from the procedure.

In recent years, there has been an expansion in the use of laparoscopic surgery in urology [17,18]. This has further reduced the number of open procedures from which tissue can be harvested. However, it is technically feasible to obtain tissue samples at laparoscopic operations, particularly bladder neck from laparoscopic radical prostatectomy, and ureter from laparoscopic nephrectomy. We are not aware of any previous comparative study between tissue harvested laparoscopically and that obtained from open operation.

MATERIALS AND METHODS
Tissue was harvested from consenting adults undergoing open or laparoscopic radical prostatectomy (for bladder neck muscle), open or laparoscopic nephrectomy (for ureteric muscle), and open cystectomy (also for ureteric muscle). The study had ethics committee approval. Bladder neck was obtained from eight patients who underwent open radical prostatectomy, and 11 who underwent laparoscopic radical prostatectomy. Ureter was obtained from seven patients via laparoscopic nephrectomy, while nine underwent open nephrectomy or nephroureterectomy. Ureter was also obtained from seven patients undergoing open cystectomy. For transport to the laboratory, harvested tissue was immediately placed into cold (4 °C) oxygenated Krebs’ solution (buffered with 95% O2/5% CO2), containing [in mmol/L] Na+ 137, Ca2+ 2.5, Mg2+ 1.2, Cl− 133.6, PO4− 1.2, HCO3− 25, glucose 101.0, and 16.6% glucose solution (dextrose 5%).
Muscle strips dissected from the samples were suspended in a Brading-Sibley organ bath, and superfused with warm (37 °C), oxygenated, buffered Krebs’ solution (Fig. 1) [19]. Using four organ baths, four muscle strips from each patient were studied simultaneously. The strips were pre-tensioned to 0.5 g and after 60 min of equilibration, they were stimulated using standard agonists, at the concentration that produced a maximum response in physiologically responsive tissue. These were determined (unpublished data) as 100 µmol/L carbachol in Krebs’ solution for 15 s for bladder neck muscle, and 100 mmol/L KCl-enriched Krebs’ solution for 4 min for ureteric muscle. The use of these agonists to contract ureteric and bladder smooth muscle is well described [5,20–24]. Tensions produced were recorded using strain gauges and acquired using data-acquisition software. Data were processed on computer and statistically analysed using a commercial package. Samples in which there was a contractile response were considered to be physiologically responsive. The two-tailed Fisher’s exact test was used to determine significance and \( P < 0.05 \) deemed to indicate significant differences. Samples from each group (i.e. open or laparoscopic, bladder neck or ureter) were sent for histological analysis, and all analysed by one histopathologist unaware of the origin or treatment.

RESULTS

Openly harvested bladder neck muscle from six (of eight) patients showed a measurable response to the standard agonist (Fig. 2a), and laparoscopically harvested bladder neck from only two (of 11) patients had any measurable response; this difference was statistically significant (\( P = 0.024 \)). Openly harvested ureteric muscle from 12 (of 16) responded to stimulation (Fig. 2b), while only one (of seven) laparoscopically harvested muscle samples responded; this was also statistically significant (\( P = 0.019 \)).

Histological analysis of resected muscle showed abnormalities in some strips, i.e. perinuclear stranding and loss of cell borders (Fig. 3). These abnormalities were present in muscle strips taken by both resection methods, and there was no correlation between resection method and histological abnormality.

DISCUSSION

As noted, the laparoscopic approach is being increasingly used in modern surgery; this may have implications for the availability of human smooth muscle from the urinary tract for physiological experimentation. The present results showed a significant reduction in the yield of reactive tissue harvested laparoscopically compared with that obtained at open operation. Thus the increasing use of the laparoscopic approach will further reduce the availability of urological smooth muscle for experimentation. Another implication of these results is that any measurable response seen in laparoscopically harvested muscle may not be applicable to normal tissue, as it is from a population that is significantly different from openly obtained samples.

We have noted that diathermy may be used more prolifically in laparoscopic dissection than in open resections, because of the greater need for a bloodless field and the difficulty in using other ‘open’ methods of haemostasis, e.g. pressure application and vessel ligation. No quantitative studies comparing the electrocautery current used have been published, but other authors have also postulated an increased use in laparoscopic than open surgery [25], and the hazards of laparoscopic electrocautery are well described [26]. If there is greater use of diathermy, electro-coagulative damage may explain the poor response of laparoscopically resected muscle to agonists.

On light microscopy, perinuclear stranding and loss of cell borders (Fig. 3) were seen in muscle from both resection methods. Possible causes of these abnormalities might include diathermy injury, poor fixation or ischaemia. Thus, the histological assessment was unable to confirm any increased diathermy-specific changes in the laparoscopically obtained samples. However, this may be because of the short interval between the use of any diathermy near the resection specimen and the subsequent fixation of the tissue, before histological changes have become manifest. Also, damage giving rise to unresponsiveness may be subcellular, e.g. by denaturation of proteins, or disruption of intracellular organelles or cytoskeletal elements, and thus not visible at a light microscopic level. Nevertheless, other investigators have also found poor physiological results in smooth muscle exposed to diathermy current, such as prostatic chips from TURP (C. Fry, personal communication, 2004). Further work, such as electron-microscopic analysis, may provide a correlation between cellular abnormalities and physiological effects.
responsiveness, but this is outside the scope of the present study.

The primary objective of any operation is the increased well-being of the patient, not the harvest of urological tissue for experimentation. It would therefore be inappropriate to modify best surgical technique to suit research requirements. However, it is important for researchers in this field to be aware of the impact that the increase in laparoscopic surgery will have on the availability of appropriate tissue for physiological experimentation. Also, researchers should question whether any laparoscopically harvested urological smooth muscle behaves in vitro in a fashion representative of normal human physiology.

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CONFLICT OF INTEREST

None declared.

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An Asia-Pacific revolution?

Over the last three decades we have seen the impact of Asia-Pacific on the pharmaceutical marketplace. The rise of the Japanese pharmaceutical industry is well documented and its impact on the healthcare environment is spread across many therapeutic areas. In a urological context, two companies (Takeda and Yamanouchi) have made particularly important contributions, having been heavily involved in the development of leuprolide, tamsulosin and more recently solifenacin. Although the Japanese industry was considered to be reactive rather than proactive, highly successful drugs can result from this model of operation; tamsulosin, the world’s sixth α-blocker, has become the market leader for treating BPH, capturing 35–40% of a $2 billion market. This inward investment into established Japanese companies migrated to western companies, resulting in joint ventures (e.g. TAP) that have now established their place as multinationals in their own right. In parallel, any cost benefit of undertaking R&D has been eroded as companies have sought or established R&D facilities in other countries with lower capital and staffing costs. Although there has been some degree of pharmaceutical industrial activity in both Singapore and Korea, few drugs have reached the market from these sources. In comparison, several Indian companies, e.g. Dr Reddy, Lupin Laboratories and particularly Ranbaxy, appear to have been much more successful [1], with drugs that have reached the marketplace and produced relatively healthy pipelines. Based on these attributes, Ranbaxy have signed a deal to develop drugs for GSK; have successfully licensed a BPH drug (pamirosin) to Schwarz; and have two other drugs for urological disease in Phase II. This is a record that many larger companies would like to emulate. However, a major issue remaining in Indian R&D is that of the protection of intellectual property.

Nevertheless, the relative success of Indian companies has partly been driven by the low cost-base for research in the country and, more recently, the cost savings that can result from undertaking Phase I and II clinical development. This has been coupled with a return to the national pharmaceutical industry of many highly trained expatriate postdoctoral scientists who have considerable experience within large pharmaceutical companies. There is some evidence that a similar trend is occurring within China (PRC).

One of the disadvantages of operating within Indian has been the lack of a cohesive strategy from central government (it could be argued by some, particularly the ABPI, that this is a positive advantage!). This is not the case in China, where there appears to be an integrated private equity and central funding strategy. Prime examples are the creation of the China National Pharmaceutical Group (www.sinopharm.com) and CapitalBio Corporation (www.capitalbio.com).

This has not precluded the rise of smaller entrepreneurial business units such as Galaxaco (sic), Comman Pharmaceuticals and The Shanghai Animal Laboratory. The common feature of these and other companies is the influx of resources (funding and trained manpower from the West). There is no reason why they should not be as successful as similar companies operating in Japan and India. Given the cost-base in China, the return to the investor, be it high net worth individually or ‘big-Pharma’ building for the future, is likely to be considerably greater than elsewhere. However, will any of this affect the discovery and development of urological drugs?
In some instances the therapeutic focus is obvious, e.g. Comman are focusing on cardiovascular and metabolic disorders; whereas the Shanghai Animal Laboratory is operating as a CRO, covering pre-clinical safety evaluation, toxicology and Phase I to Phase II; my company, Plethora Solutions (www.plethorasolutions.co.uk) has a primary interest in sexual medicine in China; Sinopharm and CapitalBio have a wider brief, covering many therapeutic areas and involving the traditional western approach to synthesising novel chemical entities coupled to the traditional Chinese approach of working with natural products. It is the latter approach that is most exciting and could produce therapies that extend well beyond any one specific disease. At this point any reader who subscribes to the mantra of evidence-based medicine usually switches off and I am left with a few psychosexual counsellors. Although, as we are aware from Internet sales, clinical evidence is not a prerequisite for short-term commercial success, ultimately well-designed clinical trials are. This ensures product registration in the major markets and increases the probability of securing patents. Investors in Chinese companies involved in natural-product development are equally aware of the advantages of adopting western standards.

Most companies involved in natural-product research also use extracts that are well-characterised (by gas chromatography/mass spectroscopy-based ‘fingerprinting’). This has the considerable advantage that bulk supplies of the individual ‘ingredients’ can be reproducibly obtained (often synthetically or at least semi-synthetically, c.f. antibiotic synthesis). Equally, it allows a considerable degree of patent protection and minimises the possibility of ‘pirating’ in most major markets. Although the development of a natural product extract is more complex than a traditional novel chemical entity, assuming that all the regulatory steps are followed it will be straightforward. The approval of taxotere and Serenoa repens extract in several countries represents similar analogies. However, the problem, particularly with S. repens, is that not all brands are equal [2].

A common misconception is that the regulators require a precisely defined mechanism of action. Taxotere is defined as a microtubule inhibitor; how precise is that? S. repens extract – what is it? How does it work? Do we even really understand how α-blockers produce their effect? Indeed, with certain drugs e.g. chlorpromazine, the polypharmacology is probably required to produce the clinical benefit. No, at least in a clinical context, what the regulators actually require is a good benefit-risk ratio and consistency of response.

In Nanjing, one company at least has evaluated two ‘fingerprinted’ extracts in patients with BPH or erectile dysfunction, using validated instruments (IPSS and International Index of Erectile Function) in ‘reference standard’ clinical trials (double-blind, placebo-controlled, crossover studies, 12 weeks per leg, 4-week washout, 120 men per group). In parallel, interactions with nitrates and α-blockers have been examined. Although there have been some issues relating, not surprisingly, to linguistic validation, data are sufficiently compelling apparently to initiate similar studies in Europe. Let us hope that a shortage of patients who are fluent in both Croatian and Mandarin does not compromise recruitment!

Next month I will examine the impact of changing guidelines and pricing on andropause therapy.

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Modified specimen retrieval facilitates urethro-vesical anastomosis in laparoscopic radical prostatectomy

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INDICATIONS
Laparoscopic radical prostatectomy (LRP) has now been formally accepted as a treatment option for localized prostate cancer [1]. In this procedure, the interval after complete excision of the prostate to its removal through a port-site depends on the time taken to complete the urethrovesical anastomosis. Surprisingly, a survey of published reports on both the transperitoneal and extraperitoneal techniques gave little information on precisely how to deal with the prostate before its extraction [2–12]. As appropriate handling of the prostate can facilitate the final and crucial part of the procedure, we describe a technique developed in our department over the last 5 years.

METHOD
Our technique of extraperitoneal LRP was described previously [6]. After transecting the membranous urethra the prostate is immediately placed in an Endocatch bag (United States Surgical Corp., Norwalk, CO, USA), introduced through the right iliac fossa 11-mm port, and the handle and the string of the Endobag are brought out through the port. A graduated palpation probe (Fig. 1) is then passed through the same port (Fig. 2), which is removed (Fig. 3) and then replaced to its original position by railroading onto the palpation probe (Fig. 4). This simple manoeuvre positions the string and the Endocatch bag outside the port, thus freeing the port for subsequent passage of laparoscopic instruments. By tightening the string, the entrapped prostate can be positioned just underneath the right iliac fossa port-site, allowing ample space for urethrovesical anastomosis with ease in the pelvis.

Between 1999 and 2004 this technique was used in 220 extraperitoneal LRPs, with the detailed results reported elsewhere [6,13]. The manoeuvre takes ≈30 s, and there were no complications or difficulties.

COMPARISON WITH OTHER METHODS
In previous reports of the duration between complete excision of the prostate and removing it through a port site, the prostate is described as either being left in the abdominal cavity, or immediately put in an extraction bag placed intracorporeally [2–12]. In reality this period poses several problems. First, the prostate may occupy significant space in extraperitoneal LRP, and may physically interfere with making the urethrovesical anastomosis. Second, leaving the prostate in the abdomen runs the theoretical risk of cancer-cell seeding. Third, in the transperitoneal approach, the prostate or the
Endocatch bag containing the prostate must be moved from the retropubic space to the peritoneal cavity; it may therefore not be possible to easily locate the prostate at the end of the procedure, and even then it takes time to extract the full length of the string of the Endocatch bag through the port before specimen extraction is possible.

An experienced laparoscopist may be able to directly replace the port without using a palpation probe; nevertheless, difficulty can be encountered in a muscular or obese patient. Additional finger-dilatation of the tract to facilitate replacing the sheath may produce leakage from the pneumoperitoneum or pneumo-extraperitoneum, requiring additional suturing or clipping of the skin.

ADVANTAGES AND DISADVANTAGES

The present technique not only avoids cancer-cell spillage but also allows quick replacement of the port and immediate secure positioning of the prostate to facilitate subsequent removal. It creates ample space for the anastomosis to be made and takes little time. Although this manoeuvre is of special benefit in extraperitoneal LRP, which has become the preferred approach in several experienced European centres [6,14–16], the technique is equally applicable to the transperitoneal approach and for other laparoscopic oncological procedures, e.g. laparoscopic partial nephrectomy and laparoscopic radical cystectomy.

The key device in this technique is a palpation probe, which is used by general surgeons in laparoscopic cholecystectomy, and in gynaecology during various laparoscopic gynaecological procedures. Our combined experience confirms it to be a safe instrument for intracorporeal use. The principle of combining the laparoscopic port and the palpation probe is similar to using a JJ stent with a guidewire. To this end, we therefore always include this relatively inexpensive palpation probe (cost 70 Euro) in our urological laparoscopic set.

With the recognition of LRP as a treatment option for prostate cancer, and the increasing preference for the extraperitoneal approach [6,14–16], we recommend including this easy, safe and reliable technique in the options for laparoscopic urology.

CONFLICT OF INTEREST

None declared.

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Use of a pedicled rectus abdominis muscle flap to protect against fistula formation after bladder neck closure

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INDICATIONS
Long-term urethral catheterization is often used in the management of the female patient with a neuropathic bladder. This mode of management can be associated with several common problems. Urine leakage might continue around the catheter despite the use of different catheters or anticholinergic therapy, or the catheter might be expelled from a small, contracted or overactive bladder, again often of neuropathic aetiology. Catheter expulsion may be exacerbated by an ever-increasing calibre of the urethra secondary to urethral erosion. The patients are often debilitated, there are associated chronic neurological conditions, and so major nursing issues arise in relation to pressure areas and skin ulceration. Treatment options include upper tract diversion or bladder outlet closure with placement of a suprapubic catheter. The major drawback of bladder outlet closure is the relatively high incidence of restored continuity between the oversutured bladder outlet and the urethral stump, leading to continued leakage of urine [1–5]. Omental interposition in bladder neck closure might reduce this risk, but it is not always possible to mobilize the omentum to allow it to be placed in the pelvis, and this manoeuvre requires intraperitoneal exploration [2]. Here we describe a technique of tissue interposition between the bladder neck and urethral stump using a pedicled rectus abdominis muscle flap.

METHODS
Between April 2001 and December 2003, the technique was used during bladder neck closure in 10 women (mean age 64.2 years, range 49–85); the mean (range) follow-up was 9.8 (3–36) months. To date there have been no reports of urine leakage, and no recorded complications of herniation at the graft site, or rectus muscle haematoma. The technique has since been applied to the repair of colovesical and vesico-uterine fistulae in another three patients.

SURGICAL TECHNIQUE
A Pfannenstiel incision is made and the bladder exposed extraperitoneally. The urethra is mobilized above the pelvic floor and divided as low as possible. The distal urethra is oversutured with two layers of absorbable 3/0 polyglactin sutures. A suprapubic catheter is placed before closing the bladder outlet in two layers with a 3/0 polyglactin suture. A rectus abdominis muscular flap is raised using the inferior epigastric artery as a pedicle. This flap can be of varying length and width, depending on the amount of vascularized tissue deemed necessary for the procedure. The mobilized flap (Figs 1 and 2) will reach easily into the pelvis and is sutured in place over the bladder neck area with three or four 3/0 polyglactin sutures. Care must be taken not to compromise the blood supply when placing the holding sutures. A non-suction wound drain is placed and the wound closed.

COMPARISON WITH OTHER METHODS
Early reports on the management of female urinary incontinence in the current clinical setting often centred on the use of urethral rather than bladder-neck closure [3–5]. The transvaginal approach gained favour, as it was a less invasive for the debilitated patient than the suprapubic route. In an earlier series of urethral closure described by Feneley [3], 17 of 24 patients had good drainage and no leakage of urine after the initial procedure. A subsequent series by Eckford et al. [4] of 50 women with multiple sclerosis showed that transvaginal urethral closure was initially successful in only 27 (54%).

The transvaginal approach for bladder neck closure in the presence of urethral destruction was described by Zimmern et al. [6]. However, the technique has been more often described in children with severe urinary incontinence [7], where it is often coupled with the creation of a continent, catheterizable conduit. In a recent series of 20 children with a variety of neuropathic or congenital disorders, only 12 (60%) were dry from the point of view of the urethra after the initial surgery, although four leaked from the stoma [7].

Bladder outlet closure can be approached either transvaginally or suprapubically, depending on the operator’s preference. We propose that the interposition of a vascularized tissue graft greatly decreases the fistula rate after bladder outlet closure and that, in a suprapubic approach, the use of a pedicled rectus abdominus muscle flap is a simple way of achieving this with no need to enter the peritoneum. The suprapubic route is
often preferable in these patients, as lower limb contracture can make access for a vaginal approach unfeasible. The rectus muscle flap is therefore more conveniently harvested than a Martius graft, and obviates the need for a separate incision in an area frequently eroded by leakage of urine. Furthermore, this easily raised pedicled flap can reach most areas in the pelvis, and so can be used in dealing with other fistulae in this area, such as colovesical and vesico-uterine fistulae.

In conclusion, we recommend the use of this flap in all cases of bladder neck closure approached via the suprapubic route and in cases of fistula between pelvic viscera where the omentum cannot be easily mobilized. This valuable addition to the urologist’s repertoire does not appear to have been described previously.

CONFLICT OF INTEREST
None declared.

REFERENCES

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EFFECT OF INSULIN-LIKE GROWTH FACTOR-1 ON APOPTOSIS OF RAT TESTICULAR GERM CELLS INDUCED BY TESTICULAR TORSION

Sir,

Ozkurkcugil et al. [1] provided new insights into the role of IGF-I on testicular apoptosis in the rat; this study highlights very well the important role of IGF-I on testicular apoptosis but the following points need clarification. (i) During torsion of the testis, ischaemic necrosis usually occurs within 4–10 h of torsion [2]; the study did not mention the comparison of necrosis in different groups. (ii) Reperfusion injury is usually more evident where the detorsion occurs while the testis remains in the scrotum for up to 5 h [3], but in the present study the detorsion time was not mentioned. (iii) The findings in group 5 at 24 h were stated to be similar to those in group 4 at 4 h but reference to the Table shows they are not comparable. (iv) There were significantly fewer apoptotic germ cells after IGF-I and 4 h of torsion but no difference between group 2 and 5 after 24 h.

However, this study provides a useful basis to devise more effective and targeted treatment regimens in testicular apoptosis in future.

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Department of Pharmacology, Postgraduate Institute of Medical Education & Research, Chandigarh, 160012, India


SURGICAL ATLAS: THE COHEN PROCEDURE

In a recent issue of the BJU Int there was an excellent representation of the operation for ureteric reimplantation [1]. The presentation states ‘the bladder is drained either by a transurethral catheter for 5 days or by a suprapubic catheter’. We clearly showed [2,3] that catheter drainage results in patients having a longer stay and more pain; between January 1997 and February 2002, 181 children had a Cohen transstrigonal ureteric reimplantation. Medical records for these patients were reviewed retrospectively. Eighty catheterized patients before April 2000 were compared with all 58 catheter-less patients since then. Variables for comparison included analgesic requirement, complication rate, length of hospital stay and incidence of bladder spasm. The indications for surgery were primary VUR, vesico-ureteric junction obstruction and duplex systems, with or without ureteroceles, and did not differ significantly between the groups (P < 0.56). In those with no suprapubic catheter, a caudal injection of bupivacaine was given at induction and bupivacaine was also instilled into the bladder before the bladder was closed with a single layer of 3/0 polyglycolic acid suture.

None of the catheter-less patients had an epidural infusion for analgesia, whereas 56% of the catheterized patients had an epidural catheter inserted; 34% of the catheterized and 21% of the catheter-less patients required morphine for pain control, and most (78%) of the latter only required oral analgesics. In contrast, only 8% of the catheterized patients used oral analgesics as the only analgesia. The mean length of stay was 25.6 h for the catheter-less and 81.6 h for the catheterized patients. Also, bladder spasm was significantly reduced in the catheter-less patients (1.7% vs 51.3%) but the complication rate was not significantly different between the groups (P < 0.69). It is disappointing that the no-catheter approach has been used since 1981 [4], and has again been published recently, and yet is not as widely accepted in Europe.

Thank you for publishing this letter to help promote the discontinuation of pain-causing catheters.

PADDY DEWAN, Department of Urology, Women’s and Children’s Hospital, South Australia


THE PREVALENCE AND NATURE OF ORGASMIC DYSFUNCTION AFTER RADICAL PROSTATECTOMY

Sir,

I agree with these authors [1] that greater attention needs to be paid to orgasmic dysfunction rather than just concentrating on erectile function. However, this paper raised more questions than it answered. The authors used a non-validated questionnaire of which one of the questions was a visual analogue score (a type of measure which is known to be highly inaccurate). No mention is made of the format of the other 13 questions. The questionnaire, rather surprisingly, is not supplied. I think that it is usual practice, where a non-standard measure has been used, that the authors publish it. If the authors had validated their questionnaire the
See related article by Kwak et al., BJU Int 2004; 95: 565–8. Given that the authors did not report on patients undergoing radical prostatectomy in the current study, an assessment of the patients undergoing this procedure is needed to address the comparison of radical prostatectomy with other treatments. Furthermore, the paper implies that the patients were asked if their operation was nerve-sparing; was this the most accurate way of collecting this data?

RICHARD PEARCY, BAUS Senior Clinical Fellow in Andrology, designate, London, UK

1 Barnas JL, Pierpaoli S, Ladd P et al. The prevalence and nature of orgasmic dysfunction after radical prostatectomy. BJU Int 2004; 94: 603–5

REPLY

Mr. Pearcy’s comments are welcomed and appreciated. In response, the primary purpose of this work was to be provocative, which tends to generate more questions than answers. As to the unvalidated questionnaire, his comments are germane, but there does not yet exist, to the best of my knowledge, a functional inventory for assessing orgasmic function that includes an assessment of orgasmic pain and urinary incontinence. In our opinion, the current post-prostatectomy quality-of-life inventories (UCLA-PCI [1] and EPIC [2]) do not address these problems adequately. At present, validating a questionnaire is a time-consuming process requiring significant funding, virtually impossible to accomplish without society or industry funding. When venturing into a novel area such as orgasmic dysfunction after prostatectomy, there are barriers that can only be overcome with time and further exploration. We are endeavouring to refine our future assessment of men with these problems. We hope that Mr Pearcy will harness his energy and help contribute to this area through excellent research.

JOHN P. MULHALL MD, DIRECTOR, Sexual Medicine Program, Departments of Urology, Cornell Medical Center, Memorial Sloan Kettering Cancer Center, New York, NY, USA

1 Litwin MS, Hays RD, Fink A et al. The UCLA Prostate Cancer Index:

development, reliability, and validity of a health-related quality of life measure. Med Care 1998; 36: 1002

2 Wei JT, Dunn RL, Litwin MS et al. Development and validation of the expanded prostate cancer index composite (EPIC) for comprehensive assessment of health-related quality of life in men with prostate cancer. Urology 2000; 56: 899

A COMPARISON OF LYCOPENE AND ORCHIDECTOMY VS ORCHIDECTOMY ALONE IN THE MANAGEMENT OF ADVANCED PROSTATE CANCER

Reply

We appreciate the previous correspondent’s continuing interest [1] in our article [2]. The matter of the deaths of patients in the two treatment groups is well described in the results section of our paper. There were 19 (35%) deaths during the study, of which 12 were in the orchidectomy group and seven in the orchidectomy plus lycopene group. Of these, two were secondary to cardiovascular causes (one in each group). That gave an overall survival of 56% and 74% in the two groups, respectively. We appreciate your concern about the discrepancy in the text and figure (Kaplan-Meier curves) as printed. There was a problem in the figure and its legends, possibly caused by some distortion and maldjustment. The issue of legends was a problem in the figure and its legends, which may have caused an impression of a difference in the survival rates.

MOHD S. ANSARI and NARMDA P. SGUPTA


2 Ansari MS, Gupta NP. A comparison of lycopene and orchidectomy vs orchidectomy alone in the management of advanced prostate cancer. BJU Int 2003; 92: 375–8

3 Ansari MS, Gupta NP. A comparison of lycopene and orchidectomy vs orchidectomy alone in the management of advanced prostate cancer. Reply. BJU Int 2004; 94: 678

EFFECT OF CIRCUMCISION ON URINARY TRACT INFECTION AFTER SUCCESSFUL ANTIREFLUX SURGERY

Sir,

We read with great interest this article by Kwak et al. [1] describing a review of patients undergoing circumcision at the time of surgical correction of VUR. Compared with patients having antireflux surgery alone, the authors found no difference in the rates of recurrent UTI after surgery in this circumcised group (mean age 42 months). In addition, there was no difference in renal outcome for the two groups, documented by follow-up DMSA scintigraphy. Although their discussion highlighted the advantages of circumcision in preventing UTI in neonates and children (as reported by Wiswell et al. [2]), the authors conclude from their data that circumcision during antireflux surgery is not protective. Most paediatric urologists agree that circumcision is a useful adjunct in preventing UTI in boys with severe uropathy, but this is the first published study to examine this.

We previously reviewed patients at Great Ormond Street Hospital, obtaining patient records from our database with codes for uropathy (PUV or VUR), UTI and circumcision. Patients with recurrent UTI who had been circumcised as a sole therapeutic manoeuvre were selected. We found 18 patients who fulfilled these criteria over the past decade; 13 boys had PUV (of whom eight also had VUR) and five had high-grade reflux (IV or V). Before circumcision patients had had 2–5 UTIs and required 1–3 inpatient treatment episodes for infection. The mean age at circumcision was 8 months. In 12 of the boys there were no further UTIs after circumcision (follow-up 2–17 years). In the remaining six patients circumcision did not stop the UTIs, but two of these only had one further episode. All six of these ‘failures’ were in chronic renal failure (CRF) and four went on to have further major surgery (e.g. ureteric re-implantation). Of the 12 ‘successes’ only three were in chronic renal failure and none required antireflux surgery.

We disagree with the conclusions of Kwak et al.; our data present a strong argument that circumcision is an effective intervention in boys with severe uropathy whose main clinical problem is recurrent UTI. It appears to be less effective in boys with co-existent CRF. In the latter group we speculate that continued infections are contributed to by the
immunosuppressive effect of CRF and reduced urinary flow. Our patients had their circumcision when much younger than in the study of Kwak et al, and this may partly account for our different findings. To assess this question properly would require a prospective randomized study, but our institution is not alone in finding this difficult to achieve. We think that circumcision should be considered in all boys with severe uropathy as an adjunct to prophylactic antibiotics, and we routinely perform it at the same time as neonatal valve resection in boys with PUV. UTI and secondary renal damage should be prevented at all costs.

NIKESH THIRUCHELVAM and PETER M. CUCKOW, Great Ormond Street Hospital For Children NHS Trust, London, UK


A MINIMALLY INVASIVE TECHNIQUE FOR OUTPATIENT LOCAL ANAESTHETIC ADMINISTRATION OF INTRADETRUSOR BOTULINUM TOXIN IN INTRACTABLE DETRUSOR OVERACTIVITY

Sir

Botulinum toxin (BTX) is about to become a standard therapy for hyperactive detrusor and sphincter dysfunction of different origins. Sphincter injections have been used in urology mainly for treating neurogenic detrusor sphincter dyssynergia [1], but detrusor injections have been increasingly dominant in this condition for ~5 years [2]. Most users give 20–40 injections of BTX with a long needle through a rigid cystoscope. Harper et al. [3] described a minimally invasive technique in which a standard flexible cystoscope is used to spread the toxin over the wall of the bladder. As noted by them, some urologists still spare the trigone to avoid the theoretical risk of iatrogenic VUR; others include the trigone without this complication [4].

It can be difficult to see where injections have been given and which areas have been omitted. That might pose a serious problem when the injection technique described by Harper et al. is used, because orientation through a flexible cystoscope is often more confusing than orientation through a rigid cystoscope. For those who are starting with detrusor injections, we recommend using indigo carmine to mark the sites where BTX has already been applied. For demonstration purposes, we use the common dilution of 200–300 units of BTX-A in 16 mL of normal saline and add 4 mL of indigo carmine (Indigo Carmine Solution Ampoules, Paesel + Lorei, Germany) to bring the total volume to 20 mL. Each injection is ~0.5 mL. We prefer to use a systematic checkerboard pattern, which is easy with a rigid cystoscope. Indigo carmine makes it easy to see where BTX has already been administered (Fig. 1).

Using the dye shows how widely the toxin spreads immediately at the submucosal site (Fig. 1). Furthermore, it can be shown that almost no toxin flows back from the suture tracts into the bladder when it is full. In contrast, when the bladder is only half-full, there seems to be backflow into the bladder. The dye technique is not necessary in general, but for teaching or demonstration purposes, and for the first few injections, it is useful, especially when the flexible cystoscope is used.

HEINRICH SCHULTE-BAUKLOH and HELMUT H. KNISPEL, Department of Urology, St. Hedwig Hospital, Teaching Hospital of Charité University Hospital, Berlin, Germany

Surgical Atlas
Replacing the ureter by an ileal tube, using the Yang–Monti procedure

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Accepted for publication 9 December 2004

ILLUSTRATIONS by STEPHAN SPITZER, www.spitzer-illustration.com

INTRODUCTION

Long-segment defects of the ureter may result from chronic inflammatory disease (e.g. tuberculosis or bilharziasis), retroperitoneal fibrosis, iatrogenic injuries during open or endourological surgery, neoplasms and radiation damage. If the ureteric loss cannot be repaired with intrinsic urinary tract tissues, ureteric replacement is indicated. Various surgical techniques have been proposed for replacing damaged ureters, including the use of synthetic material, free autologous or pedicled grafts [1]. Except for pedicled bowel segments, most of these techniques have failed to gain wide acceptance.

The use of small bowel for ureteric replacement was described as early as 1906 [1]. In 1959, Goodwin et al. [2] reported the use of ileal ureter not only for the repair of damaged ureters but also as for recurrent urinary stones. Ileal replacement of bilharzial ureters was described by Bazeed et al. [3]. Results were generally unsatisfactory, particularly in patients with low creatinine clearance. To circumvent some of the problems and improve the functional outcome, tailoring of the ileal ureter and reflux prevention by a nipple valve was attempted [4]; the reported results showed only a marginal improvement. Nevertheless, creating the stapled nipple valve was followed by a tendency toward stone formation in a significant proportion of cases.

The feasibility of constructing a long tube from short segments of ileum was evaluated clinically [5] and experimentally [6]. The application of this procedure for ureteric replacement was explored initially in experimental animals [7]. Because the functional outcome was excellent, the technique was applied in the clinical setting. Herein, we report the technical details.
The left ureter became obstructed after a complicated ureteroscopy. The patient is placed supine position and a median laparotomy performed.
Figure 2

The paracolic gutter is incised and the descending colon reflected medially to expose the retroperitoneum. The left ureter is exposed proximal to and away from the strictured segment to avoid difficult dissection of the dense adhesions with the possibility of injury to adjacent structures. A loop is passed beneath the ureter and held up for traction, to facilitate its dissection.
Figure 3

The ureter is transected at a healthy well vascularized segment and freed cranially, taking care to preserve its blood supply. A stay suture is applied which helps later in proper orientation to avoid the possibility of any axial rotation.
Figure 4

A sufficiently wide, properly placed buttonhole is created in the left mesocolon near its base; this site is carefully selected to avoid injury of the mesocolic vessels. With the help of the previously inserted stay suture, the ureter is pulled through this window and laid intraperitoneally.
Figure 5

The intestinal substitute is derived from the terminal ileum; a segment 6–7 cm long is usually sufficient. The main operating room lights are switched off. With back transillumination, the arborization of the blood vessels within the mesentry is clearly visible. The selected segment is further subdivided into three equal parts, with preservation of the individual blood supply.
Figure 6

The isolated segments are then separated and the continuity of bowel re-established. The pedicles of the isolated ileal rings are temporarily controlled by a soft bulldog clamp.
Each ring is then incised along its longitudinal axis; the incisions of the most proximal and distal segments are not at the antimesenteric border but close to the mesenteric attachments. The incised segments are unfolded and their adjacent ends sutured together using 4/0 absorbable material.

Figure 7
Figure 8

The result is the creation of an intestinal plate of ≈2 cm wide and 16–18 cm long.
This plate is then tubularized around a 16 F Nelaton catheter using a continuous 4/0 absorbable material. The result is the formation of an ileal tube with a suitable cross-sectional diameter and of sufficient length. The ends of this tube are devoid of any mesenteric attachments, because of the asymmetric incisions of the proximal and distal rings. This facilitates anastomosis of the tube to the ureter proximally and its antirefluxive implantation in the bladder distally.
Figure 10

An end-to-end-anastomosis is now made between the cephalic end of the ileal tube and the spatulated proximal ureter. The previously inserted stay suture helps in orientation and prevents any tendency for axial rotation. The anastomosis is made using interrupted 4/0 absorbable sutures and stented using a silicone tube of suitable size (10–12 f).
The distal end of the ileal tube is then implanted into the bladder by a nonrefluxing ileo-vesicostomy, using the Lich-Gregoir principle. The bladder is moderately filled with saline solution. Exposing a 4–5 cm aspect of the bladder wall, the incision is carried out through the perivesical fascia, the detrusor muscle and down to the submucosa. The fascial muscular flaps are raised on either side by further dissection using a fine pair of scissors with a blunt tip. Care is taken to avoid injury of the underlying mucous membrane.
Figure 12

The bladder is then emptied of its fluid contents. A buttonhole is excised from the mucosa at the distal end of this trough.
A stented mucosa-to-mucosa anastomosis is then made between the vesical mucosal membrane and the distal end of the ileal tube, using interrupted 5/0 absorbable material.
Figure 14
The previously dissected flaps are joined together in front of the ileal tube using interrupted 3/0 absorbable sutures.
POSTOPERATIVE CARE

The abdomen is drained by two tubes brought out through separate incisions in the abdominal wall. The abdomen is closed in layers. Intravenous alimentation is maintained until normal bowel function resumes. Prophylactic antibiotics are administered routinely. The drains are removed once fluid drainage has ceased. The ureteric stent is removed after 12–14 days, and the urethral catheter kept for 2 weeks.

FUNCTIONAL OUTCOME

Our initial clinical experience and early results were the subject of a previous publication [8]. Excretory urography and/or MR urography showed an excellent configuration of the substitute, with no dilatation or obstruction. All the treated renal units had evidence of improvement or stabilization.

CONCLUSIONS

This new technique offers some distinct advantages. A short bowel segment is included, with the consequent absence of metabolic complications. It allows construction of an ileal ureter with a suitable cross-sectional diameter with no need for tailoring, and makes possible the use of an antireflux technique.

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### 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.

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>AIDS</td>
<td>acquired immune deficiency syndrome</td>
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<tr>
<td>ANOVA</td>
<td>analysis of variance</td>
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<td>AUA</td>
<td>American Urological Association</td>
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<td>BAUS</td>
<td>British Association of Urological Surgeons</td>
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<td>BCG</td>
<td>bacille Calmette-Guérin</td>
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<td>BPH</td>
<td>benign prostatic hyperplasia</td>
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<td>BSA</td>
<td>bovine serum albumin</td>
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<td>BOO</td>
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<td>CI</td>
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<td>digital rectal examination</td>
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<td>diethylene-triamine-penta-acetic acid</td>
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<td>ethylenediamine tetra-acetic acid</td>
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<td>gonadotrophin-releasing hormone</td>
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<td>high-pressure liquid chromatography</td>
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<td>nonsteroidal anti-inflammatory drugs</td>
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<td>PAGE</td>
<td>polyacrylamide gel electrophoresis</td>
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<td>prostate-specific antigen</td>
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<td>polytetrafluoroethylene</td>
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<td>pelvi-ureteric junction</td>
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<td>sodium dodecyl sulphate</td>
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<td>transforming growth factor</td>
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<td>tumour necrosis factor</td>
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<td>TNM</td>
<td>Tumour-Node-Metastasis</td>
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<td>TRUS</td>
<td>transrectal ultrasonography</td>
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<td>transurethral resection of the prostate</td>
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<td>UTI</td>
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| March 8–10   | 17th Saudi Urological Conference, King Fahd Medical Military Complex, Dhahran, Saudi Arabia. | Contact: Dr Ibrahim A-Oraifi, King Fahd Medical Military Complex, PO Box 946, Dhahran 31932, Saudi Arabia  
T: +966 3 844 0000 ext 4502  
F: +966 3 840 5936  
E: saudi17thurologyconference@hotmail.com or saudi17thurologyconference@yahoo.com |
| March 16–19  | XXth Congress of the European Association of Urology, Istanbul, Turkey. | Contact: Congress Consultants BV  
T: +31 26 3890 680  
F: +31 26 3890 686  
E: congress.consultants@uroweb.nl  
| April 11–15  | Urology Specialist Registrars' Spinal Injuries Course, Twice Annually. Sheffield/Wakefield, UK. | Contact: Carole Gregory (secretary to Mr P R Tophill, Consultant Urological Surgeon) Spinal Injuries Unit, Northern General Hospital, Herries Road, Sheffield, S5 7AU, UK  
T: +44 114 271 5645  
E: carole.gregory@sth.nhs.uk |
| May 3–4      | Comprehensive Urological Laparoscopy: An intermediate Level Training Course incorporating 'Different Techniques of Nephrectomy'. Course Director: Mr A. Rané. Venue: Aesculapium, Tuttlingen, Germany. | 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-academy.com |
| May 21–26    | American Urological Association Annual Meeting, San Antonio, TX, USA. | T: +1 800 908 9414  
E: convention@auanet.org  
| June 6–10    | XVIII Cuban Congress of Urology and IX Central American and Caribbean Congress of Urology in Centro de Convenciones 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 |
T: +46 31 708 60 00  
F: +46 31 708 60 25  
E: nuf2005@gbg.congrex.se  
W: http://www.scaur.org/ |
| June 11–16   | Basic Sciences for Urology Residents, Charlotte, VA, USA. | Contact: William Steers, MD  
T: 800-282-7077 / 713-622-2700, ext 82  
E: meetings@houston.auanet |
T: +82 2 569 5802  
F: +82 2 569 5803  
E: ica2005@mecci.co.kr  
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<tr>
<th>Date</th>
<th>Event</th>
<th>Contact Details</th>
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<tr>
<td>June 24-27</td>
<td>6th International Consultation on new Developments in Prostate Cancer and Prostate Diseases, Palais des Congrès, Paris, France.</td>
<td>Contact: Dr Saad Khoury, Clinique Urologique (Pr. Richard), Hôpital de la Pitié, 83 bd de l'Hôpital 75634 Paris Cedex 13, France T +33 1 42 17 71 20 F +33 1 42 17 71 22 E <a href="mailto:consulturo@aol.com">consulturo@aol.com</a> W <a href="http://www.congress-urology.org">www.congress-urology.org</a></td>
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<tr>
<td>June 25-29</td>
<td>60th Annual Meeting Canadian Urological Association, Ottawa, ON, Canada.</td>
<td>T +1 514 395 0376 F +1 514 875 0205 E <a href="mailto:central.office@cua.org">central.office@cua.org</a> W <a href="http://www.cua.org">http://www.cua.org</a></td>
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<tr>
<td>June 27-July 1</td>
<td>BAUS Annual Meeting</td>
<td>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 <a href="mailto:admin@baus.org.uk">admin@baus.org.uk</a> W <a href="http://www.baus.org.uk/">http://www.baus.org.uk/</a></td>
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<tr>
<td>July 6-9</td>
<td>31st Annual Meeting of the International Academy of Sex Research (IASR) Ottawa, Canada.</td>
<td>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 <a href="mailto:iasr@northwestern.edu">iasr@northwestern.edu</a> W <a href="http://www.iasr.org">http://www.iasr.org</a></td>
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<tr>
<td>July 28-August 1</td>
<td>XXV Biannual Congress of the Urological Association of South Africa, Sun City, Pilanesberg, South Africa.</td>
<td>Contact: Toucan Communications T +1 27 11 886 9895 F +1 27 11 886 9897 W <a href="http://www.urosa.co.za">http://www.urosa.co.za</a></td>
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<tr>
<td>August 26-September 1</td>
<td>35th Annual Meeting of the International Continence Society, Montreal, Canada.</td>
<td>T +1 847 605 0850 E <a href="mailto:vicky@icsoffice.org">vicky@icsoffice.org</a> W <a href="http://www.icsoffice.org">http://www.icsoffice.org</a></td>
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<tr>
<td>October 5-8</td>
<td>10th Biennial Meeting of the Asia Pacific Society for Sexual &amp; Impotence Research (APSSIR) Cairns, Australia.</td>
<td>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 <a href="mailto:promaco@promaco.com.au">promaco@promaco.com.au</a> W <a href="http://www.promaco.com.au/">http://www.promaco.com.au/</a> conference/2005/apssir/</td>
</tr>
<tr>
<td>December 1-5</td>
<td>SBUR 15th Annual Meeting</td>
<td>Wyndham Miami Beach, Miami Beach, FL, USA. T 847 517 7225 F 847 517 7229 E <a href="mailto:info@sbur.org">info@sbur.org</a> W <a href="http://sbur.org/meetings/future.asp">http://sbur.org/meetings/future.asp</a></td>
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