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I would like to thank the many busy people who act as referees for the Journal

The first thing I would like to do in the New Year of 2005 is to thank the many busy people who act as referees for the Journal, and who are listed at the end of this issue. It is with pleasure that I do this, understanding very well how much time each of the contributors have donated to the Journal. Without their help the organisation of the BJU International would be impossible. I am truly grateful.

I was recently in Japan, giving lectures in Tokyo, Fukuoka and Fukui. I had a wonderful time, with excellent hospitality and kindness having been given to me. I mention this because I was delighted to hear from Japanese friends how popular the BJU International is in their country. We receive many submissions of a very high quality from Japanese authors, a high percentage of which are published every year. We intend to maintain our good relationship with Japanese urologists, and have more interesting plans of which you will hear more in the future. Once again, thank you all for the excellent welcome I received there.

The second BJU International debate was held recently in London at the European Society of Sexual Medicine meeting. It was chaired by Roger Kirby, with contributions from the successful team which spoke in Buenos Aires: Jeremy Heaton, Geoff Hackett, John Dean and Ian Eardley. Once again the debate was very well attended, and I believe was enjoyed by the audience. The excellent contributions from the speakers was a combination of insightful comment and humour, presented in a very skilful manner. My thanks also to Mike Wyllie for arranging the debate, of which we have several more in the pipeline.

In a previous issue I mentioned that we would be adding a third annual prize in addition to the Bob Krane prize and the John Blandy prize. I am delighted to say that Don Coffey has allowed us to put his name to this prize, and it will be given for the best paper appearing in the Investigative Urology section of the journal in the calendar year.

JOHN M. FITZPATRICK
Editor - in - Chief
A conversation between Darracott Vaughan and Alan J. Wein

BIOGRAPHY
Alan J. Wein, MD is professor and chair of the Division of Urology at the University of Pennsylvania School of Medicine and Chief of Urology at the Hospital of the University of Pennsylvania. He is a graduate of Princeton University and received his MD from the University of Pennsylvania School of Medicine.

Dr Wein is the 1992 recipient of the Urodynamics Society Lifetime Achievement Award, the 1996 recipient of the F. Brantley Scott Award of the American Foundation for Urologic Diseases, the 1997 recipient of the Hugh Hampton Young Award of the American Urological Association, and the Distinguished Service Award of the American Urological Association in 2000. In 2001 he was presented the Distinguished Contribution Award by the American Urological Association. In 1996 Dr Wein delivered the Ramon Guiteras Lecture at the annual meeting of the American Urological Association. He has held or holds editorial positions on many well-respected journals including Journal of Urology, Urology, Neurourology and Urodynamics, the BJU International, and the Survey section of the Journal of Urology. He has been named Editor in Chief of Campbell’s Urology, acknowledged to be the most authoritative text in the field.

His fields of interest lie in urologic oncology, voiding function and dysfunction, the physiology and pharmacology of voiding function and dysfunction.

INTERVIEW
Alan, I know you grew up in West Virginia, not in a medical family, how did you get interested in medicine?
I grew up in Beckley, West Virginia. In my family it was acceptable only to become either a doctor or a lawyer. I picked medicine. I am happy that I did. As for my choice of urology, my father had some urologic problem for which he went up to the Mass General and I went up there with him. I met Wyland Ledbetter’s partner, Ed Parkhurst, who impressed me as a really nice guy who enjoyed what he did. I thought that if all urologists were this nice, because they took care of interesting things and made people happy, seems to me that might be a good thing to go into.

How old were you then?
I was young, probably somewhere in the neighbourhood of 13 or 14.

So how did you end up at the University of Pennsylvania?
When I was a kid in Beckley, if you wanted to go out of state to college it was necessary to go to a prep school. So I went to Mercersburg Academy. I was lucky to get into Princeton University. I applied to a bunch of medical schools. The fellow who came from Penn to do the interviews at Princeton had written all of the articles on the subject of my senior thesis. I was overwhelmed that I was talking to this guy, and Penn offered me a position, and I said yes and that’s how I wound up at Penn.

And then once you got to Penn you obviously had at least one brief interaction with urology through your dad. How did you pick urology as a field?
At Penn you had exposure to urology, at that time during the 3rd clinical year. We don’t anymore.

Is that good or bad?
I think it is bad for the students. I think it’s bad for urology. We had to spend two weeks on urology and I liked it. I particularly liked Harry Schoenberg who became my mentor in urology. I liked what he did and how he ran his life and how he took care of his patients. I took an elective in urology with Harry and John Murphy my senior year and that locked it up. When it came time to decide where I was going to train, I was very comfortable at Penn. I liked the institution; I liked the people. I stayed there for two years of surgery, one in the lab on a training grant and three years of clinical urology.

I think Penn had the same training grant as Virginia did. Do you think there is any chance of going back to that? Do you think that is an important thing for urology?
I thought that it was. It certainly introduced me to lower urinary tract physiology and pharmacology. At that time Penn had a dynamite pharmacology department. I got a tremendous amount of help from those folks with whom I was able to collaborate. So, for me it was very important and I think that if we went back to that, or at least if the good programs had a training grant, we would see a lot more progress in scientific issue. At least some people who do not have a thought in the world about pursuing a basic science interest would get turned on and then pursue academic interests.

Did you stay at Penn?
I did, I went into the army for two years after residency because I was in the Berry plan. I went to Ft. Benning, Georgia. I looked at maybe three or four jobs that were open but there really wasn’t any job that was better than the one that I was offered at Penn so I went back to Penn.
During that time you came up with, what I thought, was your brilliant concept of voiding disorders in a simplistic fashion with problems of storage and problems with emptying. There had been so many complex systems before that. How did you think of that?

Simple-minded people think of simple things I guess. It was actually an outgrowth of something that Brantley Scott said. Brantley wrote an article, a very obscure article that I don’t think anyone ever noticed, and the subject was a simple-minded way of looking at voiding dysfunction; in other words, failure to empty or store because of the bladder, or the outlet. What we did was to extend this so you could categorize the disease processes and all urodynamic studies into what they showed, as far as what the bladder and the outlet are doing, during filling and storage and then emptying, and then you could take all of the treatments and categorize them as to whether they affect filling/storage or emptying and whether they do so by inaction on the bladder, the outlet or both. So, you could give a whole clinical course on voiding dysfunction, whether it was neurogenic or non-neurogenic, just with that one concept.

It sure made it easier to learn. And then your work on understanding the innervation of the bladder and bladder base led to major changes in management of BPH.

I was lucky enough to have the help of Bob Levin. One thing that I believe is that you now need to have a PhD if you are going to do serious work in a field. I think that regardless of what you did in the one or two years you spend in the lab, afterwards you meet your level of competence and you have to decide whether you are going to go back and retool your technology or whether you are going to find someone who has the same interest as you do and you can take the field one step further. I was lucky to find Bob Levin, who was working in a cardiovascular pharmacology lab at Women’s Medical College but who had done his PhD work with a woman named Marilyn Hess at our place who was a pharmacologist. Bob had learned all the adrenergic and cholinergic assays as a part of his cardiovascular work. I talked to him, liked him and hired him. Bob immediately got grants when he came to Penn. It was obvious he could run his own lab and could tailor his interest to the lower urinary tract. He was with me for 18 years. He was primarily responsible for my success in that field.

Then you became chairman.

I started to direct the activities of the division in 1979 and then I became the chairman formally in 1982.

What are your accomplishments that you are most proud of?

Staying sane, that’s one! We changed the structure of the residency program a number of times to adapt to what I call, ‘contemporary educational needs’. I think that our residency program has prospered, and I’m most proud of the character and expertise of all of our finishing residents. We have been able to continue our research in lower urinary tract physiology and pharmacology. I adopted the philosophy that I had heard first from Pat Walsh, which was ‘do one thing and do it well’ as far as your basic research interest is concerned. When Bob Levin left, we changed to a molecular approach with Sam Chacko. I did not have anything to do with John Duckett’s recruitment, but John Duckett’s recruitment was very fortuitous for Penn. I always regarded John as one of the brightest people that I had ever met. He would push and prod me to do certain things that I probably would have been slower to do otherwise. I was able to attract Bruce Malkowicz to stay. Bruce is brilliant and has developed his own cancer research program with his own PhD. I guess if I had to pick out one gift it was not to make anyone angry, at least for too long, and to be able to provide the glue that holds everybody together and to be able to pretty much satisfy everyone at the medical school and at the affiliate hospitals.

Your interest in neuromodulation led you into the area of gynaecourology or urogynaecology. Where do you think you are headed in that field with respect to the gynaecologists?

As far as female urology and urogynaecology are concerned, we have seen a gradual development of a system that I think in the US right now is not entirely satisfactory. On the one hand, on the urology side, we have a number of fellowships that are excellent. But they are not accredited fellowships. On the other hand, there is an accredited fellowship sponsored jointly by the American Board of Urology and the Board of Obstetrics and Gynaecology in female reconstruction and pelvic health. Everyone who graduated from one of these fellowships has been a gynaecologist, not a urologist. There are only two urologists that I am aware of who are in those training programs, and if we are going to survive in urology, that situation has to be changed. If change occurs, it will come from SUFU (Society for Urodynamics and Female Urology) and from the American Board of Urology. The Board has agreed to try to negotiate a different arrangement with the OB/GYN whereby they can also accredit fellowships that are run by urologists. One big problem now is that some hospitals are being persuaded that unless someone is a graduate of one of these accredited fellowships, they should not and can not do things that the hospital considers to be in those areas, such as prolapse repair, vaginal hysterectomy, etc., and that would be disastrous for urology if permitted to continue.

Another new job you have is editorship of Campbell’s Urology. What changes do you see for the next edition?

It’s a real privilege to be the editor-in-chief of Campbell’s Urology. I was associate editor with you for multiple editions, and I regard that as one of my most important jobs. The upcoming edition is now entitled, “Campbell Walsh Urology” because of the contributions that Pat Walsh made when he was editor-in-chief. It will be a new format, one that I think will be very reader friendly. The publisher has agreed to put any figures that the authors want in colour, which I think is a big plus. In addition, in order to try to make it more conducive to reading, there will be a lot of colour tables, a lot of colour highlights, and a summary section of important points at the end of each relevant section. We took a hard look at the chapter organization, changed this, tried to break down the larger chapters into smaller subjects and tried to pick a number of experts, rather than one person to write a global chapter.

What else do you do when you are not doing all these things?

I like to spend time with my family, with my wife and my daughter. My daughter was just 9 and in the 3rd grade. She is a constant source of amazement and bewilderment to me and a joy as well. We like to try to take our daughter with us pretty much wherever we go. I love to play tennis but don’t get enough of a chance, as I would like. I take care of a lot of editorial responsibility, which I actually enjoy. Wish I had more time to do that with various journals. I like taking care of the matters in the division, even though some of them are fairly complicated, now more so than they used to be. I enjoy getting through a day with no matters related to work.

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INTRODUCTION

Since starting our program with robotic-assisted laparoscopic prostatectomy (RALP) at Vanderbilt University a little over a year ago, we have performed over 250 of these procedures. Postoperative pain has been minimal; discharge is usually on the first day after surgery, no patient has required a perioperative blood transfusion and the catheter is usually removed 1 week after surgery. Patients are able to return to all pre-surgical activities within a month.

By almost any standard, these are good results [1]; indeed, most reports of laparoscopic prostatectomy strongly imply, if not directly declare, that results are better than can be achieved with an open surgical incision [2,3]. Certainly, websites or marketing efforts for laparoscopic prostatectomy attempt to contrast this approach with radical retropubic prostatectomy (RRP), which is often depicted as a bloody, highly invasive procedure associated with a large surgical incision and prolonged hospital stay and convalescence.

Experienced surgeons know otherwise. When we started our programme for RALP we developed a clinical pathway for perioperative management and postoperative follow-up and instructions. We use the same pathway for patients undergoing RRP or RALP and have prospectively followed both patient groups. The first day after surgery is targeted as the anastomosis should be secure regardless of whether a patient undergoes RALP or RRP. However, we plan catheter removal for ~1 week after surgery in both groups, as the anastomosis should be secure either way. Instructions on return to activity are identical for both groups. We currently are analysing the quality-of-life surveys completed by all patients to see if any difference is noticeable for recovery and in the long-term follow-up.

RALP does not have to be a 'bloody' operation; we have reported previously a requirement for transfusion of any blood products in only ~1% of men undergoing RRP [4]. This leaves little room for improvement with RALP with regard to the transfusion requirement. There has been a statistically significant increase in discharge serum haematocrit in the RALP group, so the overall blood loss is less. However, whether the patient loses an average of 150 or 450 mL of blood is probably not clinically relevant.

We use the same pain management pathway for patients in both groups [5,6]. Epidural catheters or injections are not used and we do not use patient-controlled analgesia with intravenous narcotics. Indeed, to minimize narcotic usage, patients are given ketorolac (a NSAID) in the operating room and continued for 24 h after surgery. Supplemental oral narcotics are used as necessary. The bottom line is that patients undergoing RRP with a limited lower midline abdominal incision of no more than 8–9 cm long simply do not have much pain after surgery. The mean pain reported on a 10-point scale (1 as least and 10 as worst) is <3 for both the RRP and the RALP patients.

We use a running vesico-urethral anastomosis with RALP and five interrupted sutures with RRP. However, we plan catheter removal for ~1 week after surgery in both groups, as the anastomosis should be secure either way. Instructions on return to activity are identical for both groups. We currently are analysing the quality-of-life surveys completed by all patients to see if any difference is noticeable for recovery and in the long-term follow-up.

What then are the advantages of laparoscopic prostatectomy, whether with robotic assistance or not? By all the measures discussed above, we have been able to do just as well with RRP. Our results are potentially subject to the criticism that we are comparing prospectively an initial experience with 250 RALPs to men undergoing RRP after the author's experience with >2000 of these operations [7]. However, our results with RALP match those of any reported series. We have not found that RALP is 'less invasive' than RRP in any clinically meaningful manner.

We were not surprised by these results; indeed we did not initiate a programme for RALP and put in the necessary effort for training and gaining experience to decrease blood loss, length of stay or postoperative pain. Although all of these variables must be considered, few patients would consider them the most important outcomes after surgery for prostate cancer. Tumour control (i.e. margin status), continence and potency are the primary outcomes which will determine the role of RALP. There is reason to think that the results with these measures could exceed what can be obtained with RRP.

Although the loss of tactile feedback with RALP was an initial concern to us, observation of tissue compressibility or elasticity is a ready substitute for this. The superb visualization, minimal traction on the neurovascular bundle, and precision with which tissue can be incised and sutured may well translate into better results for RALP. We do well on each of these important outcome measures with RRP but there undoubtedly is room for improvement. We are continuing to gather data from our prospective comparative trial. Anecdotally, we are highly encouraged by our RALP results but are not yet ready to make any definitive statements, as we need a longer follow-up and more patients.
COMMENTS

The 'take-home' message is one of cautious enthusiasm for RALP, but this enthusiasm is based on realistic data and comparisons. Our results with either the open or laparoscopic procedure do not necessarily translate to other centres, and each surgeon must realistically assess their results. The perioperative morbidity with RRP has been vastly diminished and laparoscopic prostatectomy does not have much opportunity for improvement. On continence, potency and tumour control, we have good results with RRP, but have reached a plateau, and there is clearly room for improvement. Hopefully, RALP will allow us to move significantly beyond that plateau to provide even better results for our patients.

REFERENCES


Correspondence: Joseph A. Smith, Jr, Vanderbilt University Medical Center, Department of Urologic Surgery, A 1302 Medical Center North, Nashville, TN 37232-2765, USA. e-mail: debbi.cannon@vanderbilt.edu

WHAT IS THE BEST IMAGING FOR STONE MANAGEMENT?

SIMON V. BARIOL and DAVID A. TOLLEY – The Scottish Lithotriptor Centre, Western General Hospital, Edinburgh

INTRODUCTION

Controversy surrounds the choice of optimum imaging for treatment planning, as evidence for the diagnostic superiority of cross-sectional imaging for patients with acute flank pain or suspected urolithiasis increases and replaces IVU. Essential information about obstruction, pelviccalyceal anatomy, stone size and fragility, not readily available from CT, must be obtained before a rational decision can be made about outcome-based treatment. As no single imaging method provides comprehensive information about all of these factors, and very few departments of urology have access to all imaging methods, there is a need to review the imaging pathway for comprehensive stone management.

INVESTIGATION OF FLANK PAIN

Non-contrast helical CT (NCCT) is the best investigation for diagnosing acute flank pain \([1,2]\), with a sensitivity of up to 100\% and a specificity up to 98\%. NCCT is now widely available, can be rapid and detects pathology outside the urinary tract. IVU has a lower sensitivity and specificity (64\% and 92\%, respectively) for investigating suspected ureteric colic \([2]\), while providing limited information about other conditions.

ASSESSING STONE SIZE

The major predictors for spontaneous stone passage of a ureteric stone are size \([3,4]\) and position \([5]\). NCCT correctly measures the stone transverse diameter but tends to overestimate cranio-caudal length when judged by the number of 'cuts' in which the stone is seen \([6]\), because of the effect of partial volume averaging.

STONE FRAGILITY

Calcium oxalate and uric acid stones can be differentiated by CT densitometry \([12]\). Despite evidence that densitometry can predict the likelihood of fragmentation, this is not widely assessed \([13]\).

FOLLOW-UP

Stone clearance is usually assessed by follow-up plain films or ultrasonography (for renal stones). NCCT is more sensitive but results in considerably more radiation exposure. A baseline plain film is necessary if the diagnosis was made by NCCT, if standard follow-up protocols are used. If the stone is
not easily seen on the initial film there is an occasional need for further imaging with NCCT if there is no clear evidence from the patient that the stone has passed spontaneously and symptoms remain.

Although NCCT is the best investigation for establishing the presence of upper urinary tract stones, no single investigation is best at identifying all influencing factors for those patients requiring treatment, but IVU appears to be the most versatile. The outcome after SWL, more than any other treatment, is affected by the factors outlined above, but there is an increasing tendency to offer SWL without the full anatomical information available from IVU. Treatment decisions made without comprehensive radiological information will at best produce a poorer outcome and may result in inappropriate management, although the morbidity after SWL is low. The position on optimum imaging for stone management is not yet clear, and further critical analysis of available imaging methods measured against outcome is required.

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Correspondence: David A. Tolley, The Scottish Lithotriptor Centre, Western General Hospital, Crewe Road, Edinburgh EH4 2XU, UK. e-mail: datolley@baus.org.uk

OPTIMIZING THE DIAGNOSIS OF PROSTATE CANCER IN HIGH-RISK MEN: THE SUPPLEMENTARY BIOMARKER APPROACH

SASHI KOMMU, RAJ PERSAD*, NICK WATKIN†, PATRICK J. BOYD† and ROS EELES – Translational Cancer Genetics Team, The Institute of Cancer Research, Sutton, Surrey, *Bristol Urological Institute, Bristol, and †St. George’s Hospital, London, UK

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INTRODUCTION

Prostate cancer is the most frequent malignant tumour among men aged >50 years; its incidence varies according to the country of origin of the patient, and ethnic group. Known risk factors are race and a positive family history of the disease, with familial aggregation (at least two cases in the family) in ~20% of cases and a hereditary form of prostate cancer in 5% [1]. This proportion increases with younger age at diagnosis. Currently it is often recommended that PSA levels are assessed and a DRE done annually in men, starting at age 40 years, although African–American men and those with a family history of prostate cancer should have PSA tests and a DRE annually beginning at age 40 years. Another high-risk group is Afro–Caribbean men; one of the highest incidences of prostate cancer is in Jamaican men in Kingston, much higher than even in black Americans. Furthermore, the cancers in Jamaican men are more significant clinically, with greater morbidity in Jamaica than in the USA [2]. Some experts recommend screening all men at 40 and 45 years old, and then every 2 years beginning at age 50 years. The American Cancer Society [3] and the AUA [4] endorse these screening recommendations, i.e. annually from age 50 and beginning earlier for African-Americans and other high-risk groups.

High-risk men may need to be followed carefully, as the disease seems to be elusive in its presentation, often not conforming to the current PSA thresholds for diagnosis. This has not been confirmed by large-scale studies, but has been confirmed in other groups. The current high rates of false-negative TRUS-guided biopsies add to the complexity of managing these patients.
Several novel molecular targets have been identified and studied for establishing new diagnostic tools; however, African-American and indeed Afro-Caribbean men (specifically Jamaican) have the highest incidence of prostate cancer in the world. These men, those with a family history of prostate cancer and those with a combination of the two must be assessed with greater caution, so that an early diagnosis with a view to curative intent can be achieved.

There are other interesting approaches for establishing new diagnostic tools; measuring DD3 (PCA3 gene) expression using PCR, and glutathione-S-transferase-1 (GSTP1) hypermethylation. Both show promising results for their usefulness as new biomarkers. DD3 is one of the most prostate cancer-specific genes at present. Expression of the DD3 gene is a very sensitive and specific marker for detecting prostate tumour cells in a high background of normal (prostate) cells. DD3 estimates can be used clinically on prostate needle biopsies or bodily fluids (e.g. blood, ejaculate, urine or prostate fluids (e.g. blood, ejaculate, urine or prostate
massage fluid). Quantitative RT-PCR assay for DD3 bears great promise as a tool for molecular urine analysis and has great potential for reducing the number of unnecessary biopsies.

Other potential markers for prostate cancers that can be applied in this way include hypermethylation at the GSTP1 gene, using a sensitive PCR test. GSTP1 hypermethylation is present in >80% of prostate cancers but not in normal tissues or in BPH, making it a very specific marker for the disease. Methylation of the GSTP1 gene promoter region is the most common epigenetic change in prostate cancer. The quantitative GSTP1 methylation assay, a recently developed methylation-specific and PCR-based technique, allows the accurate discrimination of benign prostate tissue and prostate cancer even in small, formalin-fixed prostate needle biopsies. In addition, quantitative GSTP1 methylation also correlated with prostate cancer Gleason grade and cancer volume, suggesting that quantitative GSTP1 methylation may be of prognostic significance. The role of these methods must be validated on a large-scale basis before widespread application.

Recent studies have reported enhanced prostate cancer detection in caucasians using serum human glandular kallikrein 2 (hK2) combined with total PSA (tPSA) and free PSA (fPSA). Martin et al. [15] tried to quantify this in the African-American cohort. Independent variables and the ratios f/tPSA, hK2/tPSA, hK2/PSA and tPSA/PSA were compared between cancer and non-cancer groups. The ratio of hK2/PSA was observed to increase the positive predictive value of f/tPSA when <0.1 and 0.1–0.25; also, f/tPSA offered the best performance and highest specificity in prostate cancer detection in African-American men over the entire range of tPSA.

The authors concluded that the use of several biomarkers might ultimately increase the specificity of prostate-cancer screening in African-American men. This can potentially be extrapolated to other high-risk groups. Importantly, a better yield of cases may result from expanding tests for prostate cancer, but there is still no concrete evidence from population screening that this will make a difference to overall survival at present.

CONCLUSION

The combination of several biomarkers in addition to PSA levels can be exploited to optimize the detection rate of prostate cancer in high-risk patients. The supplementary biomarker approach should be explored further through large-scale studies. At present several studies are underway in the post-genomic and present proteomic era to develop other biomarkers not only in serum, but also in other body fluids such as urine.

PSA is a useful tool and has been indispensable in the management of prostate cancer, but issues have been raised about its suboptimal performance in some instances. The answer may not lie in one biomarker but may depend on identifying the cumulative association of several supplementary biomarkers with prostate cancer. This supplementary biomarker approach needs to be validated by further studies.

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Correspondence: Sashi Kommu, Translational Cancer Genetics Team, The Institute of Cancer Research, Sutton, Surrey, UK. e-mail: Sashi.Kommu@icr.ac.uk
IDIOPATHIC SHORT PENIS: MYTH OR REALITY? NICOLA MONDAINI and PAOLO GONTERO – Departments of Urology, University of Florence, and *University of Piemonte Orientale, Novara, Italy

HOW SHOULD PENILE SIZE BE ASSESSED?
Throughout history penile size has been a matter of great debate among men. In recent years this topic has become a healthcare problem, given the increasing number of patients seeking urological advice for a so-called ‘short penis’. The penis must be measured along its dorsal side, from the pubic-penile skin junction to the tip of the glans. Length is always recorded while the shaft is flaccid, before and after fully stretching it. There is no need to obtain penile dimensions during erection as the stretched flaccid penis provides a reliable estimate of the erect size [1,2].

The circumference is usually measured at the middle of the shaft. A tape measure is all that is needed to assess penile dimensions.

WHAT IS A NORMAL PENILE SIZE?
Table 1 [1,3–5] lists the reference values for penile length from the main studies in which the above standardized assessment method was used. Despite a substantial agreement in mean values across most studies, the definition of the lower normal limit is still a matter of debate. Wessells et al. [1] considered a normal penis to be of any length within the 2 SDs of the mean, i.e. according to their data a normal penis should have a flaccid length of <4 cm or a stretched length of <7.5 cm. Ponchietti et al. [3], in a large series of Italian military conscripts, expressed penile dimensions as ‘percentiles’, with 9 cm in flaccid length and 12.5 cm in stretched length falling in the 50th percentile. By assuming the 25th percentile as threshold they found, as did Wessells et al. [1], that <4 cm for the flaccid penis and <7 cm for the stretched penis were below the normal range. As a result of this arbitrary assumption, they estimated that at least 5000 young Italians in the same age range were affected by a pathological short penis. They concluded that 4 and 7 cm should not be taken as an absolute standard to define a pathological situation that needs treatment, but be interpreted in the light of other variables, like the body mass index, which correlates strongly with penile size [3].

DOES ETHNICITY MATTER IN THE DEFINITION OF A NORMAL PENILE LENGTH?
Interestingly, there is no scientific background to support the alleged ‘oversized’ penis in black people. Mean penile flaccid length and stretched length recently reported in 123 Korean military men were indeed lower than other values on non-Asian populations [5] (Table 1). At present, in the absence of any comparative study, these values remain debatable, but the possibility of racial differences in penile size should not be overlooked when investigating patients complaining of a short penis.

DO WOMEN BOTHER ABOUT PENILE LENGTH?
Of women interviewed in a recent study [6], 20% stated that the length of the penis was important and 1% deemed it ‘very important’. Opinions about penile girth followed a similar trend, although length appeared less important than girth (21% vs 32%, respectively). The women who found the girth of the penis important had the same opinion about the length of the penis. In the end, only a small proportion of women respondents gave substantial importance to the size of the penis. Again, these values may be used to reassure patients in a clinical setting.

HOW SHORT IS THE PENIS OF PATIENTS SEEKING A TREATMENT FOR PENILE LENGTHENING?
Most if not all the men who seek penile lengthening surgery are likely to overestimate a ‘normal’ penile length, i.e. they have the so-called ‘dysmorphophobia’, a falsely reduced image of an otherwise normally proportioned penis. We drew this conclusion after assessing 67 consecutive patients, with a mean age of 27 years [7], presenting to us and requesting a penile lengthening procedure. None of them could be classified as having a pathological short penis according to our nomogram [3]. Most patients found the use of a nomogram to show them how they compared with other men helpful, and we advocate such a demonstration as a valid tool for any men asking an opinion on penile lengthening surgery.

IS PENILE LENGTHENING SURGERY EFFECTIVE?
The term ‘lengthening phalloplasty’ summarizes a small group of surgical procedures aimed at elongating the shaft, mainly in the flaccid state. The most common techniques to lengthen the penis (that combines the sectioning of the penile suspensory ligament, infrapubic liposuction and a V-Y or Z plasty of the suprapubic skin) provide only rudimentary results and a high rate of dissatisfaction in the patients [8].

However, the pericavernous apposition of autografts is widely used to enlarge penile girth and it is not unusual for the urologist to see disastrous results from this type of surgery. In a recent technique of augmentation phalloplasty bilateral saphenous grafts were used to increase the corpora cavernosal girth, thus providing a ‘true’ penile enlargement during erection [9]. Apart from this last exception, surgical penile augmentation remains a controversial issue, dominated more by opinion than a scientific background.

WHEN SHOULD UROLOGISTS USE PENILE LENGTHENING SURGERY?
In our opinion surgery, if any, must be preceded by a thorough clinical approach that we would summarize in three steps:

(i) Take the penile dimensions (flaccid and stretched length plus a measurement of the girth);
(ii) Compare the results using a nomogram [3] or reference values, like those reported in Table 1;
(iii) Counsel the patient; a straight explanation focused on the poor scientific evidence for any treatment being effective, and that any surgery must be viewed as...
experimental and unlikely to significantly enhance the erect penis, may convince some patients to forego a lengthening procedure.

For those persisting in requesting treatment, an opinion from a psychosexual counsellor is highly recommended. Finally, a more open view should be directed at conservative methods of penile lengthening. Despite that the so-called ‘penile stretchers’ have been on the market for a long time, there are at present only peer-reviewed abstracts on their efficacy [10]. Theoretically, there is no reason to believe that a penile stretcher may be less successful than surgery in elongating the suspensory ligament. Also, the use of noninvasive options gives the opportunity of widening considerably the indications for a treatment that, in most cases, is merely cosmetic.

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Correspondence: Paolo Gontero, Department of Urology, University of Piemonte Orientale, Italy. 
e-mail: gontero@med.unipmn.it
Neuroprotective strategies in radical prostatectomy

JONATHAN D. SCHIFF and JOHN P. MULHALL*
Departments of Urology, *Memorial Sloan Kettering Cancer Center and Weill Medical College of Cornell University, New York Presbyterian Hospital, New York, USA

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INTRODUCTION
Prostate cancer is the most common malignancy among men in Western society. In the USA alone, 200,000 men were diagnosed with prostate cancer in 2003. Of these, 45% will undergo radical retropubic prostatectomy (RP) for definitive local therapy [1]. While this procedure is successful for long-term disease control, the attendant morbidity secondary to urinary control and erectile dysfunction (ED) may be burdensome to the patient. Before Walsh and Donker’s [2] initial description of the anatomical RP, ED was an invariable consequence of RP. Since then numerous centres have reported potency preservation rates of >75% in men undergoing bilateral nerve-sparing surgery (NSS) [3–5], but results vary greatly among institutions and surgeons [6]. Assessing erectile function after RP is further complicated by the lack of a standardized definition of ED. While most urologists who specialize in sexual function accept the National Institutes of Health consensus conference definition of ED, this standard is not widely used in studies after RP. Data collection also varies among studies, some relying on telephone interview by the physician or a direct interview, while others use one of the currently available validated self-reported patient questionnaires. Furthermore, the advent of phosphodiesterase type 5 inhibitors and their success after RP has increased the difficulty in assessing spontaneous erectile function after RP. This mini-review focuses on four strategies, two of which may be considered preventive, i.e. NSS and intraoperative cavernosal nerve stimulation, and two which may be considered therapeutic for patients in whom nerve damage is suspected or deliberate, i.e. cavernosal nerve interposition grafting and pharmacological neuromodulation.

NSS
Since the initial description of the anatomical RP and the elucidation of the course of the cavernosal nerves, many urologists have been trained in NSS [2]. The variability in the anatomical location and distribution of these nerves, combined with variations in NSS technique and nerve handling, has resulted in variable outcomes of erectile function. Reports from centres of high volume and excellence (generally single-institution and one-surgeon series) have cited ED rates after RP of 15–40% [3–5]. However, including studies of other multi-surgeon and multi-institution experience, ED rates as high as 91% after RP have been reported [7–11]. This variability reflects the difficulty in studying erectile function after RP.

It is irrefutable that the nerve-sparing status of RP is predictive of the recovery of erectile
function; bilateral nerve-sparing is associated with better spontaneous and oral therapy-assisted erectile function than unilateral nerve sparing, which in turn is more likely to lead to functional erections than non-NSS [3,12–16]. However, the definition of nerve sparing is somewhat arbitrary. The term ‘nerve sparing’ generally refers to the macroscopic preservation of the cavernosal nerves and, while rarely reported quantitatively, there are clearly degrees of nerve sparing depending upon the amount of nerve handling.

Stretching and electrocautery used during the RP is partial injury to a cavernosal nerve on one side bilateral or unilateral nerve sparing? Different surgeons may grade identical degrees of nerve manipulation differently, and postoperative erectile function may be the only reliable surrogate of intraoperative nerve preservation. In the final analysis, with a good NSS technique, erectile function, both natural and medication-assisted, is more likely to be preserved than if the nerves cannot be spared. The question may be raised as to whether NSS should ever be used in men with ED before RP. We think that the ability of these men to respond to oral therapy after RP depends largely on cavernosal nerve integrity, and we therefore urge oncologists to consider, where appropriate, NSS in patients who are interested in sexual function after RP, irrespective of their erectile function beforehand.

INTRAOPERATIVE Cavernosal NERVE STIMULATION

Nerve identification is sometimes difficult before and/or after the extirpation of the prostate, because of patient anatomy and/or intraoperative bleeding [17,18]. Intraoperative cavernosal nerve stimulation may aid in overcoming such difficulty and may translate into improved recovery of erectile function after RP. This technique was initially described by Lue et al. [18] and formally developed as an intraoperative tool (CaverMap, Bluetooth Technologies, Ashland, MA) for nerve stimulation and tumescence monitoring [19]. The tip of the electrode is placed over the (suspected) cavernosal nerve and a biphasic current applied with increasing stimulation intensity from 1 to 20 mA [20]. The nerves are usually stimulated at many sites along their course, either before and/or after RP. Tumescence is monitored by the presence of a penile strain gauge, which records changes in penile girth.

The initial experience reported by Klotz et al. [21] found that its use before prostate removal resulted in no apparent improvement in erectile function at 1 year after RP (71% in the neurostimulated vs 62% in the standard group). However, in that initial study, using nocturnal penile tumescence monitoring, the neurostimulated group had a significantly greater duration of penile rigidity, by >60% (16 vs 2 min). Currently, most authorities experienced in nerve-sparing RP find little merit in using the device for identifying the cavernosal nerve before removing the prostate. In the analysis of Klotz et al. [21], applying the neurostimulator after prostate removal was predictive of the recovery of erectile function (68% of those with bilateral positive responses vs none of those with no response regained erectile function at 6 months after RP). This study has been criticised for a lack of standardization (nine surgeons participated), having few evaluable patients and a short follow-up.

However, further experience suggested that the use of intraoperative neurostimulation may not improve potency outcome. The Brendler group [22] examined the potency results of 60 consecutive preoperatively potent patients using intraoperative neurostimulation. The authors found a 77% rate of tumescence using stimulation after the prostate was removed, but only an 18% potency rate with a unilateral positive response, and 27% with a bilateral response at a mean of 1 year after RP. In that study, all men with no response to neurostimulation bilaterally had no functional erection after RP. Chand et al. [23] examined men who underwent RP with either bilateral NSS or bilateral neurovascular bundle (NVB) resection, coupled with intraoperative neurostimulation. Twenty-two men had a wide resection of the NVBs and all were impotent after surgery. During RP, 16 of 22 had no response to neurostimulation, but six did. Forty-one men had bilateral NSS and 27 were potent at 1 year of follow-up; 30 of these 41 men had tumescence on intraoperative neurostimulation, with 24 of them potent after RP. The intraoperative tumescence response predicted the subsequent potency ($P = 0.017$).

Recent data (Rabbani F, Eastham JA, Kattan MW, Scardino PT. Predictive value of neurostimulation, unpublished data from Memorial Sloan Kettering Cancer Center, 2002) showed no return of potency at 1 year if there was no response on either side during RP, a 46% return rate with a unilateral and an 88% rate with a bilateral response to neurostimulation. Notably, these values include men potent when using oral sildenafil. However, the specificity of intraoperative neurostimulation has been questioned in a recent multi-institutional trial [24]. A group of highly experienced surgeons reported a high sensitivity of 88% but a low specificity of 54% when using the CaverMap device. The authors suggest that this lack of specificity hampers the ability to judge what is safe to resect, or to determine which tissue needs to be preserved during RP. Despite that study, it is likely that assessing nerve function using this technique will continue to be explored at selected centres and that, with further refinements in the technology, improved computer data generation and a greater understanding of the implications of the data, intraoperative neurostimulation may soon have a role in predicting at least the return of a response to oral therapy after RP. What is clear is that failure to elicit a response on either side will probably mean no return of spontaneous erectile function after RP.

CAVERNOSAL NERVE INTERPOSITION GRAFTS

Resection of the NVB may be indicated in patients with advanced unilateral or bilateral disease (multiple positive cores, length of positive core, high Gleason grade, suggestion of extracapsular extension on imaging) to decrease the risk of positive surgical margins, the latter increasing the chance of treatment failure. Extracapsular extension increases the risk of a positive margin and this occurs most frequently in the area of the NVB. A wide resection, which may include the NVB, decreases the risk of a positive surgical margin but increases the chance of ED after RP without some intervention to restore the continuity of the nerves [25].

The initial experience using nerve grafts was in rodents, over a decade ago [26–29]. The initial clinical experience in 12 men in whom bilateral cavernosal nerves were resected, first using the genitofemoral and later sural nerve grafts, indicated that erections sufficient for sexual intercourse occurred in a third of patients, partial erections in 42% and erections with sildenafil in half [30]. A follow-up study of 28 men who had bilateral cavernosal nerve resection showed that 26% had spontaneous, medically unassisted
erections sufficient for intercourse, while the overall potency rate was 43%, including patients who had erections rigid enough for penetration when using sildenafil [31]. Another report included patients who had both unilateral and bilateral sural nerve grafts. Of the 69 patients who had bilateral NNV resected with no grafting, none recovered potency [4], but of those with bilateral sural nerve grafts, 43% were potent with sildenafil [25]. Among men with unilateral nerve-sparing combined with unilateral nerve grafts, 78% reported good potency, compared with 79% of men who had bilateral NSS [32,33].

Cavernosal nerve grafting is associated with few complications, limited to the morbidity associated with harvesting the sural nerves (genitofemoral nerve harvesting has no significant morbidity), e.g. incisional pain and hyposthaesia over the lateral aspect of the dorsum of the foot (a problem that most patients do not complain of) and increased operative time. Given the association between bilateral cavernosal nerve resection and long-term failure to obtain spontaneous functional erections or a significant response to oral therapy, this technique appears to be a reasonable strategy to restore erectile function in men in whom bilateral nerve resection is either planned or is required during RP. Thus, in the small group of men in whom bilateral cavernosal nerve resection is required, we think it is appropriate to offer cavernosal nerve interposition grafting. Whether unilateral nerve grafting has a similar impact remains to be seen, but with the patient who is acutely interested in erectile function after RP, the surgeon should consider discussing the potential advantages and minimal disadvantages of unilateral nerve grafting. Larger, randomized, multi-institutional studies will be required to definitively address the role of nerve grafting in the management of patients with RP.

PHARMACOLOGICAL NEUROMODULATION

Neural regeneration is the mechanism by which erectile function improves over time after RP. While the degree of neural trauma that occurs during RP is a determinant of the long-term recovery of neural function, biological factors involved in neural regeneration are probably important determinants of the completeness of neural recovery. Furthermore, these biological factors are likely to be a major reason for variation among individuals in erectile functional recovery after this operation. Neurotrophic factors are molecular signals that promote nerve cell survival and maintain target organ function by facilitating axon regeneration [34]. Various nerve growth factors have been implicated in animal studies of penile nerve function [28,29,35,36]. Recently, rat models of cavernosal nerve injury have been developed that have facilitated the study of neuroprotective and neuroregenerative agents.

Immunophilins are molecules found in both immune and neural tissue, although they are found in far greater quantities in the latter. The immunophilin ligand FK506 can prevent axonal degeneration and preserve electrically induced penile erections in the rat [37]. This agent is an immunosuppressant that has been used in transplant medicine for several years [38]. Other non-immunosuppressant neuromodulators have also been explored in animal models [39]. In models of stroke and neurodegenerative disease, FK506 has potent neuroprotective effects. In the rat cavernosal-injury model, FK506 treatment preserved erectile function and cavernosal nerve architecture, and appeared to be better than a novel non-immunosuppressant agent, GPI-1046 [40,41].

A recent study examined the effect of FK506 and GPI-1046 on rats that had had the cavernosal nerve injured [41]; rats treated with either FK506 or GPI-1046 had significantly greater recovery of erectile function than those treated with saline. Electrically stimulated maximum intracavernosal pressure and rate of tumescence were better in the treated rats than in controls. In that study, FK506 appeared to produce better functional results than GPI-1046. These preliminary results suggest an emerging role for direct pharmacological neuromodulation after cavernosal nerve injury. Randomized, controlled trials are underway in the USA assessing the peri- and postoperative administration of such drugs in patients after RP.

CONCLUSIONS

The primary step in ensuring satisfactory erectile function for the patient after RP is to use a careful nerve-sparing technique. Whether nerve sparing is achieved with or without intraoperative neurostimulation, preserving the cavernosal nerves is crucial to the recovery of erectile function. While several studies suggest that the intraoperative neurostimulation response predicts subsequent erectile function, it has until now failed to receive widespread acceptance or use. Similarly, cavernosal nerve interposition grafting has received a lukewarm reception from on oncologists and sexual medicine practitioners alike, probably because of the merits of the currently available data and the logistical issues involved in the grafting. It is too early to tell what the future role of pharmacological neuromodulation may be in these patients but data from animal models are encouraging. In the future, we think that a multifaceted approach to neuroprotection and regeneration for the patient after RP will be used, involving strategies to protect corporal smooth muscle, endothelium and the cavernosal nerves.

CONFLICT OF INTEREST

John Mulhall is a paid consultant to Pfizer, Lilley ICOS, Bayer GSK.

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Correspondence: John P. Mulhall, Weill Medical College of Cornell University, New York Presbyterian Hospital, 525 E 68th Street NY, NY 10021, USA. e-mail: jpm2005@med.cornell.edu

Abbreviations: RP, radical retropubic prostatectomy; ED, erectile dysfunction; NVB, neurovascular bundle; NSS, nerve-sparing surgery.
The importance of patient perception in the clinical assessment of benign prostatic hyperplasia and its management

SUNG JOON HONG, WALTER RAYFORD*, LUC VALIQUETTE† and MARK EMBERTON‡

Department of Urology, Yonsei University College of Medicine, Seoul, Republic of Korea, *Louisiana State University Health Sciences Center, New Orleans, Louisiana, USA, †Department of Surgery (Urology), University of Montreal, Montreal, Quebec, Canada, and ‡Institute of Urology, University College London, London, UK

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INTRODUCTION
BPH is a common disorder of ageing men, occurring in 19–30% of men aged >50 years [1,2], and is therefore a significant contributor to the daily practice of urologists and primary-care physicians. Furthermore, this problem is expected to increase as a result of the growing proportion of the elderly in the general population. Clinical BPH is defined as at least two of the following: moderate-to-severe LUTS (IPSS ≥ 8), an enlarged prostate (≥30 mL) and a decreased peak urinary flow rate (Q\text{max} < 15 mL/s).

LUTS describe a combination of storage (irritative) symptoms, e.g. nocturia, increased urinary frequency and urgency, and/or voiding (obstructive) disturbances, e.g. decreased and intermittent force of stream and hesitancy. Considerable evidence has confirmed the chronic nature of BPH and the risk of disease progression, characterized by increases in prostate volume, deterioration in Q\text{max} and LUTS, episodes of acute urinary retention (AUR) and the need for BPH-related surgery.

For the clinician to adequately consider the needs of individual patients with BPH, understanding the benefits and adverse effects of therapy, and gaining an insight into the impact of the disease on the patient and his partner, is critical. The aim of this review is to evaluate the impact of BPH on patients and their families.

BPH FROM THE PATIENTS’ PERSPECTIVE
While symptoms and symptom severity are important determinants of healthcare-seeking behaviour, one study suggests that ‘bother’, frequency of symptoms and interference caused by symptoms are the factors that drive men to consult a physician [3]. Another study suggests that worry and embarrassment about urinary symptoms are key in determining consulting behaviour [4]. Severely bothersome nocturia, dysuria, daytime repeat voiding, wetting clothes and urgency independently predict decreased patient satisfaction with their urinary condition [5]. Men with moderate-to-severe symptoms report, on average, 4–6 times the degree of bother and interference with their daily activities and twice the level of worry than men with mild symptoms [6]. The patient’s perception of the bothersome nature of symptoms, rather than merely their presence or absence, is therefore an important consideration in disease-specific measures of health-related quality of life (HRQoL).

Several community surveys have shown that QoL measures correlate more closely with irritative symptoms (frequency, urgency or nocturia) than with obstructive symptoms (weak stream, hesitancy, etc.) or objective measures (urinary flow, prostate volume, etc.). This suggests that irritative symptoms have a greater negative effect on patients’ QoL [7,8]. In a Scottish community-based study, half of men with BPH reported interference with at least one living activity (e.g. the ability to sleep, participate in outdoor sports or to travel). Furthermore, almost 20% of men of working age with BPH reported that urinary dysfunction interfered with at least one of their daily living activities most or all of the time. This degree of interference was experienced by only 3% of men in the same age group without BPH [9].

About 30% of men with BPH (compared with ~15% of men without) would limit their intake of fluids before bedtime or before travel, or avoid places that may not have toilet facilities (Fig. 1). This may significantly compromise the QoL of these men and their families, as well as hinder working practices and the performance of the affected man [10]. Further European research reported that the aspects of QoL most negatively affected are lack of sleep, anxiety and worry about the disease, outdoor mobility, leisure, daily activities, sexual activities and satisfaction with sexual relationships [11].

Using validated generic (not disease-specific) health profiles, e.g. the Short Form (SF)-36 or EuroQol, several population-based studies have assessed the effect of BPH and LUTS on general health status. Increasing symptom severity was associated with worsening physical role, social functioning, vitality, mental health and perception of general health, whereas the increasing bothersome nature of BPH/LUTS was associated with worsening of all dimensions of general health status and QoL [12].

One population-based study showed that the impact of symptoms on QoL domains is altered by the presence of comorbidities. In the entire study population, severely bothersome urinary symptoms were associated with a reduction in QoL in three domains (social function, role-emotional and mental health), but there was no association with physical functioning and general health perception when controlling for disease states. However, in men with no comorbidity, urinary symptoms were substantially related to physical functioning and general health perceptions [13].

In a further study in New Zealand, the scores of each of the eight domains of the generic SF-36 questionnaire for men aged 45–64 years and ≥65 years, awaiting a prostatectomy, were compared with those from the general population. Men aged...
≥45 years awaiting prostatectomy had significantly lower HRQoL in the domains of role-physical, bodily pain, general health perception, social functioning, role-emotional and mental health (Fig. 2). In addition, men aged ≥65 years also had significantly lower vitality (reduced social functioning and decreased mental health) [14].

In a UK study, men classed as being of low priority for TURP were asked to complete the Nottingham Health Profile and the EuroQoL (measuring mobility, self-care, usual activities, pain/discomfort, anxiety/depression) at the time of entry onto the TURP waiting list, and again 6 months later. There was a deterioration in all domains except social interaction, although the degree of social interaction for the BPH patients was lower than that of healthy elderly men. The most notable deterioration was in the ‘energy’ domain of the Nottingham Health Profile. The EuroQoL also tended to show deterioration over a 6-month period in mobility, self-care, usual activities and pain dimensions of patients with BPH. For the EuroQoL tariff [a composite score], there was a significant worsening of HRQoL over the 6 months of observation, from 0.83 to 0.77 [15].

THE IMPACT OF BPH ON QoL COMPARED WITH OTHER CHRONIC DISEASES

The use of the SF-36 and EuroQoL generic questionnaires enables comparison among different diseases. Using the EuroQoL, Fig. 3 compares moderate and severe LUTS with two other chronic conditions: BPH has a similar impact on HRQoL as epilepsy requiring surgery, and asthma [16–18]. Figure 4 compares chronic obstructive pulmonary disease (COPD) using the SF-36: in all domains except physical functioning, patients with BPH had a worse QoL than patients with COPD (those not presenting with an exacerbation) [19,20]. Further SF-36 data show that LUTS have a similar effect on mental health and general health as suspected peptic ulcer, varicose veins, low back pain and menorrhagia [12]. Mozes et al. [13] showed a notable negative impact of urinary symptoms on the mental health domain of QoL, which was greater than other disease states such as lung disease.

However, generic QoL questionnaires may not capture certain elements of health status of particular relevance to men with BPH. For example, the SF-36 does not directly enquire about sleeping patterns, the quality of sleep or embarrassment resulting from health status, all of which significantly affect both the patient and his family.

SEXUAL FUNCTION

Sexual function is considered an important aspect of QoL but no consensus has been reached on whether there is a distinct
relationship between LUTS and sexual function, or whether the two are merely common occurrences among middle-aged and older men. However, some studies have shown that sexual dissatisfaction increases with increased severity of LUTS. In the ICS-BPH international study of men aged ≥45 years who reported to one of 12 clinics, >70% of men of any age group found that the effect of LUTS on their sex lives was a problem, and 45% reported that their sex lives were spoiled by LUTS. Storage symptoms, in particular incontinence, had a greater association with sexual dysfunction than voiding symptoms, a finding concordant with the ICS-BPH UK community study [21]. In contrast, a French community study of men aged 50–80 years reported that symptoms of hesitancy, straining, reduced stream and wet underclothes were most strongly associated with sexual dysfunction [22].

The UrEpik study showed that erectile dysfunction, defined as a score of 0–4 using O'Leary's Sexual Function Inventory (which addresses sexual drive, erections, sexual problem assessment and overall satisfaction), was more likely in men with an IPSS of 8–35 than in those with a lower symptom score (odds ratio 1.39, 95% CI 1.23–1.92) [23]. None of these studies answer sufficiently the question of whether sexual dysfunction is directly related to LUTS or whether the two are merely common occurrences among older men.

However, the potential for BPH treatment options to positively or negatively affect sexual function should be considered and fully discussed with the patient. In one study assessing libido, sexual activity, erection capacity and rigidity after BPH therapy (surgery, α-blockers or finasteride), 66% of patients showed no change in these variables, while 20% reported positive and 11% reported negative changes [24].

FEAR OF AUR AND SURGERY

An average 60-year-old man has a 23% risk of developing AUR if he lives to the age of 80 years [25]. AUR results in prostatectomy in 24–42% of men in Britain and North America, and patients who avoid surgery with a successful trial without catheter are at high risk of requiring surgery within a year [26,27]. Furthermore, a UK audit showed that men who have a prostatectomy as a result of AUR have a greater risk of perioperative complications and of death at 30 days (relative risk, RR, 26.6), and 90 days (RR 4.4) after surgery than those who undergo elective surgery for symptoms alone [27]. The percentage of patients requiring transfusion or a second operative procedure was also greater in those undergoing initial vs elective surgery as a result of AUR (P<0.001, Fig. 5) [27].

Recent data confirm that the potential for AUR and/or surgery is a major concern to patients with BPH [28,29]: 57% of patients were significantly concerned about the prospect of AUR, and 67% about surgery, while 68% felt that the insertion of a catheter would have a worse impact on their QoL than surgery [28]. A patient survey in France investigating expectations and perceptions of 5α-reductase inhibitor therapy showed that patients were most concerned that treatment should reduce the risk of major urological complications and the need for surgery (88% and 93%, respectively). Improving symptoms and QoL were rated as secondary [29].
OBJECTIVES AND PATIENT PREFERENCES FOR BPH MANAGEMENT

Traditionally, therapeutic management in BPH has focused on improvements in symptoms and urinary flow rate. However, the focus is shifting towards reducing the risk of AUR and the need for surgery. Baseline PSA levels and prostate volume are considered in treatment decisions because of increasing evidence showing their effect on the risk of disease progression [30,31]. In a study from the USA designed to assess the effect of an educational programme to facilitate shared decision-making for selecting BPH treatment, patients were presented with the risks and benefits of watchful waiting and surgery [32]. As a result of a stated preference to avoid surgery, the investigators recommended that men with moderate-to-severe symptoms should be fully informed of their treatment options. The consequence of this study was a shift in preference from prostatectomy, as shown by a subsequent reduction in the rate of surgery [33]. The conclusions to be drawn from these data are first, the well-being of patients who are fully informed can be increased by involving them in treatment decisions, and second, BPH surgery is a treatment option, but also a risk that some patients may prefer to avoid in the short- and long-term.

In a discrete-choice experiment (an attribute-based method of data collection and analysis), a questionnaire was administered to 211 men aged >40 years randomly selected from the UK general population. Respondents were willing to wait up to 8 months for an improvement in symptoms if the treatment they received reduced the risk of surgery by an absolute 1%, and up to 2 months if they could experience an absolute 1% reduction in the risk of AUR [34]. These results show that the patient’s perception of his disease, its symptoms and complications, is crucial in determining appropriate treatment decisions that rely on shared decision-making and adequate information flow between the patient and doctor.

BPH FROM THE PARTNERS’ PERSPECTIVE

Almost all partners experience some morbidity as a consequence of the patient’s condition, with the most common concerns being disturbed sleep (28%), psychological burden (66%), inadequate sex life (48%), fear of prostate cancer (62%) and fear of surgery (62%) [35]. Limited social life, difficulty performing tasks outside the home, and pity for the patient are also frequently reported [36]. The most negative scores were those related to cancer and fear of prostate surgery, and the extent of partner morbidity correlated well with the patients’ symptom severity. In an international epidemiological study of urinary diseases in the general population, men and their partners were administered the IPSS, the SF-12 (a short version of the SF-36), and the BPH Impact Index [37]. The physical and mental components of HRQoL were negatively associated with the frequency of LUTS in their partner. However, the magnitude of the effect on the woman is smaller than the effect of LUTS on the patient.

CONCLUSIONS

BPH is prevalent among older men and has a greater negative effect on most domains of the SF-36 than COPD (in patients not presenting with exacerbation). Three crucial components of BPH should inform management decisions: it is a progressive disease for many men; BPH symptoms and their impact on the patient are heterogeneous and therefore the effect of the disease from the patient’s perspective should be elicited; and the patients’ preferences for treatment options should be considered.

Patient perceptions are receiving greater emphasis as part of clinical decision-making. The variability of relationships between symptom severity and the likelihood that the symptoms will be bothersome implies that reliance on an aggregate symptom score alone will not capture the true impact of symptoms in individual men. Rather, treatment success will depend on improvements in the aspects of the disease that are of most concern to the patient. To factor patient preference into treatment decisions, the physician should be able to adequately inform the patient of the benefits and risks of the appropriate treatments. Selecting an inappropriate treatment, or not including the patient’s preference, may lead to a cascade of therapies and unmet expectations, and increase the economic and human burden of the disease.

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Correspondence: Professor Sung Joon Hong, Department of Urology, Yonsei University College of Medicine, 134 Sinchon-dong, Seodaemun-gu, Seoul 120–752, Republic of Korea. e-mail: sjhong346@yumc.yonsei.ac.kr
Abbreviations: Qmax, peak urinary flow; AUR, acute urinary retention; HRQoL, health-related quality of life; SF, Short-Form; COPD, chronic obstructive pulmonary disease; RR, relative risk.
Robotic urological surgery: a perspective

PROKAR DASGUPTA, ADAM JONES* and INDERBIR S. GILL†

Guy’s and St. Thomas’ Hospitals and GKT School of Medicine, London, *Royal Berkshire and Battle Hospitals, Reading, and †Section of Laparoscopic and Minimally Invasive Surgery, The Cleveland Clinic Foundation, Cleveland, Ohio, USA

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INTRODUCTION

We appear to be heading towards a digital surgical future; high-tech minimally invasive surgery and more recently robotics are examples. Despite these surgical advances it is important to keep things in context. The robotics technology branch at the NASA Johnson Space Center has developed a humanoid robot called Robonaut, with dexterity approaching that of a suited astronaut. This robot can serve with human astronauts in a rapid-response capacity [1]. Compared to such technological advances, robotic urological surgery is still in the early phases of development.

The concept of automation is credited to Aristotle, from the 4th century BC [2]. The word robot is derived from the Czechoslovakian robota, which means worker. It first appeared in Karel Capek’s play, Rossum’s Universal Robots, in Prague in 1921. A surgical robot is regarded as a computer-controlled manipulator with artificial sensing that can be reprogrammed to move and position tools to carry out a range of surgical tasks. The most advanced surgical robots currently are ‘master-slave systems’ where the surgeon controls robotic arms remotely from a console. Some have argued that these are therefore not true robots, as they lack automation, and have preferred the term ‘computer-assisted surgery’ for operations with these machines [3]. This debate will continue for some time, as we are many years away from having a true robot such as the Robonaut in surgical practice.

THE MACHINES

Several robotic systems have been described, either in prototype form or clinical practice. At the time of writing there are three main robotic systems in urological practice: the da Vinci™ (Intuitive Surgical Corp., Sunnyvale, CA), the AESOP (Computer Motion, CA, now Intuitive Surgical Corp) and the PAKY-RCM (URobotics, Baltimore, MD).

The da Vinci is the state-of-the-art robotic surgical system, and until recently its competitor was the Zeus robot, but a corporate merger in 2003 resulted in Intuitive Surgical acquiring the rights to both machines. The Zeus is being phased out, making the da Vinci, with its superior performance, the unchallenged master-slave system. The basic principle involves control of three robotic arms (two for instruments, one for a three-dimensional, 3D, camera) by a surgeon seated at a console. A fourth arm for instruments has now been added. The surgeon’s finger motions are intuitively translated into movements of the robotic arms, which incorporate ‘endowrist’ technology, with six degrees of freedom (DOF). Surgical motions are enhanced by filtering of tremors and motion scaling. The 3D camera provides x6–10 magnification [4]. The main competition to the da Vinci system can be expected from ‘mechanical manipulators’, which can be used as traditional laparoscopic instruments, and are cheaper. Most of these are in the developmental stages [5].

The AESOP, which allows automated six DOF control of the laparoscope, was introduced in the mid-1990s. Many laparoscopists now regard it as part of the standard operating set-up for laparoscopic radical prostatectomy (RP). Laparoscopic images with the AESOP are steadier, with fewer camera changes and inadvertent instrument collisions than an inexperienced human assistant [6].

Wickham (cited in [2]), in association with Imperial College London, initially developed a five DOF robot for percutaneous nephrolithotomy (PCNL) that could target a calyx to within <1.5 mm. The PCNL robot currently in clinical use is the percutaneous access robot (PAKY-RCM) developed in 1996, and superseded by the Tracker in 2002 (URobotics). The PAKY-RCM has six DOF and can be used with fluoroscopy or CT guidance to improve the accuracy of needle placement. It can be combined with a Smart needle (modified from a percutaneous access needle) to measure bio-impedance and confirm percutaneous access [7].

ROBOTIC UROLOGY

ANIMAL EXPERIMENTS

In a landmark study, the prototype Green Telepresence Surgery System (SRI, International, Menlo Park, CA) was used to perform nephrectomies, cystotomy closures and ureteric anastomoses [8]. Robot-assisted laparoscopic pyeloplasty in swine, using the Zeus system, achieved a watertight anastomosis in five of six animals [9]. Robotic laparoscopic nephrectomy required significantly longer than conventional laparoscopic nephrectomy (85 vs 39 min), as did robotic adrenalectomy vs pure laparoscopic adrenalectomy (51 vs 32 min). The same group went on to compare the da Vinci and the Zeus systems on 14 pigs, reporting that the learning and operating times during nephrectomy, adrenalectomy and pyeloplasty were shorter with the da Vinci system. In that study the technical movements appeared more intuitive with the da Vinci system [10].

CLINICAL APPLICATIONS

TURP: We owe the introduction of robotics in clinical urology to Wickham and his colleagues; in the late 1980s a collaborative venture between the Mechanical Engineering department at Imperial College and Guy’s Hospital, London, saw the development of a TURP robotic frame. The resection was based on a potato model of the prostate and developed into the Probout [11], a robot with automated prostate recognition using ultrasonography, and capable of performing TURP or prostatic vapourisation. Preliminary
results showed a significant improvement in symptoms and peak flow rates [11].

PCNL, nephrectomy and adrenalectomy: After initial reports regarding its efficacy in pigs and humans, regular clinical use of the PAKY-RCM arm is underway, with the Johns Hopkins series of 23 patients undergoing robotic PCNL being compared to patients undergoing conventional manual PCNL. Robotic insertions compared favourably for time to access, number of attempts and estimated blood loss [12].

The first clinical robot-assisted nephrectomy used the Zeus system; the operative time was 200 min and the estimated blood loss <100 mL. The da Vinci robot was used for percutaneous nephrectomy in 12 patients with adrenal tumours (one right, one left; tumours 4.5 and 3 cm). The operative time was 110 and 165 min, the blood loss 50 and 100 mL, and the hospital stay 2 and 3 days [13].

A combination of the da Vinci robot and hand-assisted laparoscopy was used for live-donor nephrectomy in 12 patients. The median operative time was 166 min, blood loss 68 mL, warm ischaemia time 79 s and hospital stay 1.9 days. None of the recipients had delayed graft function [14]. An interesting case of open kidney transplantation with da Vinci robotic assistance has been reported. Vascular and ureteric anastomoses were made robotically, with a total operative time of 178 min, and excellent allograft perfusion and function [15].

Robot-assisted pyeloplasty has been reported in adults and children, using 5-mm instruments in the latter. In nine patients undergoing Anderson-Hynes pyeloplasty with the da Vinci robot the mean operative time was 139 min, suturing time 62 min, and all were successful at a short mean follow-up of 4.1 months [4]. This group compared robotic Anderson-Hynes and Fengerplasty to conventional laparoscopic pyeloplasty in 12 patients, and found robotic procedures to be quicker, as was suturing [16].

RP

In no other procedure has the clinical expansion of urological robotics been more profound than RP, largely through the contributions of Menon’s team from Detroit. Initial pioneering reports from European centres showed prolonged operative times of 315–450 min in groups of 10 patients or fewer. The Detroit experience clearly indicates that once learned, the outcomes of robotic surgery improve. It has been suggested that for established open surgeons the training for robotic RP may be somewhat shorter than for pure laparoscopy. In >300 robotic RPs the operating time was 120–180 min, with a mean blood loss of 150 mL. None of the patients needed a blood transfusion [17]. This compares favourably with an operating time of 232 min, blood loss of 370 mL and a transfusion rate of 5% after laparoscopic RP [18]. Over 95% of RP patients were discharged within 24 h. The median specimen Gleason score was 7 and tumour volume 7 mL. At 6 months, 96% of patients after robotic RP were continent and 80% of initially potent men had unassisted intercourse. In comparison, 93% continence and 86% potency rates after open RP using patient-reported quality-of-life surveys were achieved in the best hands [19]. Robotic RP costs >$150 more than open RP, but in recent months, costs have favoured robotic surgery, as the operating times decreased [17].

In their unrandomized comparison of 200 robotic with 100 open RPs, the Detroit team reported similar operative times and none of the patients needed a blood transfusion after robotic RP, compared with 67% after open RP. There were four times as many complications after open RP [20]. In their single-centre experience, the hospital stay was 1.2 days for robotic, 1.3 days for laparoscopic and 3.5 days for open RP; the respective catheter duration was 7, 8 and 15 days [17], although with a continuous suturing technique for the urethrovaginal anastomosis, the catheter duration after robotic RP has reduced to 4 days [21], similar to laparoscopic RP in other centres [18]. Experienced open surgeons have also tried to reduce the catheter duration to 7 days in >75% of their patients [22], although this is still longer than that reported after laparoscopic and robotic RP. In Detroit, positive margins were reportedly more frequent after open surgery, at 23% for open and 9% for robotic surgery [20]. Notably, the technique of evaluating pathological margins appeared to be different in the two groups. While the open cases had step-section microscopic examination of the prostate specimen, as is routine at most institutions, in the robotic group periurethral soft-tissue biopsies were evaluated on frozen sections, which may have served to ‘reduce’ the apical positive margin rate. In comparison, expert open [23] and laparoscopic [18] surgeons have reported positive surgical margins of 12.8% and 13.7%, respectively.

Cystectomy

The initial robot-assisted laparoscopic radical cystectomy and Hautmann neobladder was performed in a 58-year-old man, with an operative time of 8.5 h and blood loss of 200 mL [24]. The Detroit group reported robot-assisted nerve-sparing radical cystoprostatectomy and urinary diversion. The specimen was retrieved through a 5–6 cm incision which was then used to create either an ileal conduit or neobladder by open surgery. The neobladder was sutured to the urethra robotically. The mean blood loss was <150 mL and the margins were negative in all 17 patients [25].

Sural nerve grafting: With the da Vinci system sural nerves were grafted after RP in three potent men, aged 48, 49 and 59 years. The harvested nerve was grafted robotically using 4–6 interrupted perineural 6/0 or 7/0 polypropylene sutures. The mean operative time was 6.5 h, of which 1.5 h were for nerve grafting [26]. The current follow-up showed a return of potency in two men, one with bilateral grafts.

Other procedures: Augmentation cystoplasty has been performed with the da Vinci system but no data are currently available [4].

Trans-oceanic telerobotics

Telementing in urology has been pioneered by the Baltimore group, who have telementered several procedures in Austria, Singapore, Italy and Germany, including laparoscopic adrenalectomy, radical nephrectomy, varicocelectomy, renal cyst ablation and PCNL [27]. Telerobotic control is conducted using ISDN lines; Internet connections can also be used and are cheaper. The concept of having a surgeon in one country performing an operation in another via a computer-assisted link became reality in 2001, when a laparoscopic cholecystectomy was performed on a patient in Strasbourg by a surgeon in New York (Lindbergh operation) [28]. The time delay can significantly affect surgical performance, but if the lag time is
<700 ms the surgeon can learn to compensate.

RANDOMIZED CONTROLLED TRIAL OF TELEROBOTICS

To our knowledge the only randomized controlled trial of telerobotics in urology was the recent transatlantic study between Guys Hospital and Johns Hopkins. Statistical analysis with adequate power required a total of 304 telerobotic PCNLs, which could not be ethically supported in humans and was legally unacceptable in animals in the UK. A specially designed and validated kidney model was used (Limbs and Things, Bristol, UK) and either a robotic arm or a urologist (152 procedures each) inserted a percutaneous needle. Thirty remote procedures were performed from Baltimore via four ISDN lines. The trial showed the robot to be slower but more accurate than humans. All urologists made fewer needle passes while using the robotic arm. A cross-over trial subsequently showed that the robot can be controlled equally well from the UK to USA as it is in the opposite direction [29].

ADVANTAGES: PERCEIVED AND REAL

The perceived advantages of robot-assisted surgery include precise movement of the robotic arms, endorivist technology and 3D stereoscopic vision. For the novice, robotics seems to make intracorporeal suturing easier than in pure laparoscopic surgery. The ‘fulcrum effect’ in conventional laparoscopic surgery, whereby the instrument tips move in the opposite direction to the surgeon’s hand around the port site (fulcrum) is counter-intuitive. Conversely robotic movements are intuitive, where the instrument tips move in the same direction as the surgeon’s hands. However, experienced laparoscopic urologists feel that these are not true advantages of robotic surgery and can easily be overcome by the rigorous practice of conventional laparoscopy. Most laparoscopic surgeons, although seeing objects in 2D on a flat screen, think in 3D. They are also able to suture effectively and precisely intracorporeally with no need for a robot [3]. To be good at laparoscopic surgery requires hard work and application, but that is true for anything in life. Even robotics! To justify its expense and establish its position firmly in urology, robotics must be better than open surgery and conventional laparoscopy, not just equal. Evidence as to whether an experienced laparoscopic urologist can improve the operative skills and outcomes using robotics is not available. However, robotics provides some real advantages; the surgeon’s seated position at the console is more ergonomic; motion scaling can be a helpful computational adjunct. These machines make remote surgery possible, in principle allowing a patient at a remote location to receive care from an experienced surgeon [29]. Finally, robotic technology is sure to improve even further in future.

DISADVANTAGES

The costs of installing a robotic system, its subsequent maintenance and the price of disposable instruments currently border on the prohibitive. Pressures on healthcare funding differ greatly among countries and this is reflected in the distribution of surgical robots. It is anticipated that the price of these robots will decrease, and savings for patients and hospitals because of the advantages offered by robotics will ultimately balance the initial expenditure. Current robotic systems lack tangible force-feedback. The da Vinci is a large machine that may possibly become smaller in the future. Any improvements must be introduced as upgrades, as buying a complete new system may be financially unacceptable for many. The instrument size and design needs to be improved and the tools themselves need to last longer. Finally, although some robots such as the AESOP can facilitate solo surgery, this has negative implications for the training of juniors, who need to learn camera and instrument manipulation as part of their laparoscopic skills.

KEEPING UP WITH THE JONES’S

Owning a robot because your neighbour has one is almost fashionable, but a rather expensive prospect. Marketing expertise should not be the driving force for this technology. Instead, the drive to acquire these machines should stem from a true desire for robust scientific evaluation. This should involve not just urologists but health economists and social scientists. The Jet Propulsion Laboratory at the California Institute of Technology has formulated a new technique for evaluating human-robot system performance, which involves complex mathematical methods [30]; a similar method could be used to evaluate the true performance and safety of surgical robots.

OUR VIEW OF THE FUTURE

Surgical robotics has a bright future, but rigorous scientific evaluation is necessary. Biomedical, ethical and moral issues need to be addressed now to avoid an uncontrolled and unprepared future [31]. Legal and licensing barriers will need to be overcome before telesurgery becomes clinically viable. Shared responsibility for robotic failures needs to be in place for telerobotic procedures. As surgeons we may become too engrossed with new technology and forget our patient’s desires and satisfaction, which need assessing by validated patient-satisfaction surveys.

We have come a long way since the initial enthusiasm for urological robotics [32]; good quality evidence is at present lacking. In addition to expert opinion, prospective data comparing robotic to conventional open and laparoscopic surgery is mandatory. Randomized trials may not be possible because of patient demand, but should at least be attempted. It is anticipated that nanotechnology will enter the field of surgical robotics, but the basic principles of flexibility and adaptability of instruments and their design to suit a variety of procedures need to be maintained. Robotics is rapidly becoming a part of the operating room of the future and should be seen not as a revolution, but a well-grounded evolution [33].

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Correspondence: Inderbir S. Gill, Head, Section of Laparoscopic and Minimally Invasive Surgery, Glickman Urological Institute, The Cleveland Clinic Foundation, 9500 Euclid Avenue/A100, Cleveland, Ohio 44195, USA. E-mail: gilli@ccf.org

Abbreviations: RP, radical prostatectomy; 3D, three-dimensional; DOF, degrees of freedom; PCNL, percutaneous nephrolithotomy.
Celestial bodies and urinary stones: Isaac Newton (1641–1727) – health and urological problems

EDWARD OSTAD and GILBERT J. WISE
The Division of Urology, Maimonides Medical Center, Brooklyn, New York, USA
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INTRODUCTION

Isaac Newton was a remarkable physicist and mathematician of the 17th century. He overcame significant urological ailments, including possible nephrotic syndrome, urinary calculi and BOO while establishing his scientific genius. We assessed publications about Newton, and review his work and medical problems.

CHRONOLOGY OF NEWTON’S LIFE

Isaac Newton was born on Christmas day 1642 in Woolsthorpe, Lincolnshire, England. His father died before his birth, hence he was known as a ‘posthumous’ baby. Isaac Newton was presumably premature, as he was small enough to fit into a ‘quart pot’ [1]. Four years later, his mother married a 63-year-old man named Barnabas Smith, a wealthy rector from nearby North Witham. For 7 years young Isaac was entrusted to the care of his grandmother. He was small for his age, lonely and abandoned. He attended the local school, where he studied the Bible and arithmetic tables. At an early age he became aware of changing shadows in relation to the sun’s positions and time. Later, in Woolsthorpe, he constructed sundials that became a source of time-keeping [2].

Following his step-father’s death in 1653, his mother returned to Woolsthorpe, but Newton did not return to her domicile until he was 17 years old. During that interval, he studied in Grantham, a town 8 miles (11 km) distant, and boarded with an apothecary. He subsequently returned to Woolsthorpe and studied at the King’s School, the headmaster of which, Mr John Stokes, provided courses in Latin, Greek, Hebrew, theology and practical arithmetic that included algorithms for surveying and measuring fields.

On 5 June 5 1661 Newton matriculated at Trinity College Cambridge. His financial resources were limited and he therefore became a ‘subsisar’, which provided work and pay for his expenses. He had enough resources for his immediate needs, i.e. a chamber pot, candles for long nights and notebooks with blank pages [2].

By 28 April 1664 Newton was elected a scholar and he began making mathematical entries. In 1665, Newton received his Bachelor’s degree but had to leave Cambridge because of the plague epidemic. It is during these years that Newton began questioning and exploring issues of motion.

From 1666 to 1667 Newton remained at Cambridge, where on 2 October he became a minor Fellow of Trinity College. His work entitled Enumeratio curvarum deals with the earth’s curvature. He continued work in mathematics and astronomy. By 23 February 1669, Newton described his first telescope in a letter to Henry Oldenburg, first Secretary of the Royal Society. On October 29 of that year, Newton became the Lucasian Professor of Mathematics.

In the 1670s Newton became a Fellow of The Royal Society, based on his work in developing the reflecting telescope. In 1675 he attended his first meeting of the Royal Society, where he met Robert Boyle (1627–1691), a British natural philosopher and theological writer, a pre-eminent figure of 17th century intellectual culture, whose scientific work covered many areas including hydrostatics, physics, medicine, earth sciences, natural history and alchemy [3].

Newton presented his hypotheses on light before the Royal Society. In 1679, Newton’s mother died and he spent much of the year in Woolsthorpe. During the 1680s he observed Halley’s Comet, and in August 1684 he met with Edmond Halley (1656–1742), an English astronomer and mathematician who was the first to calculate the orbit of the comet later named after him. He is also noted for his role in the publication of Newton’s Philosophiae Naturalis Principia Mathematica which discusses the path of planets in relation to mathematical concepts. Newton began work on his Principia, a treatise of mathematics, and from 1686 through to 1687 he wrote and presented to the Royal Society three volumes of the Principia.

In 1689 Newton sat for a portrait by Sir Godfrey Kneller [1646/1649–1723], the leading portraitist in England during the late 17th and early 18th centuries [3]. Isaac Newton and the noted philosopher John Locke (1632–1704) engaged in a prolific correspondence dealing with ‘corruptions of the scriptures’.

In 1696 Newton was appointed Warden of the Mint and moved to Jermyn Street House in London. The next year Newton provided a solution to the ‘Lion’s Paw’ problem presented by Bernoulli, and his solution was read anonymously to the Royal Society. By the end of the 17th century Newton had numerous achievements; he was elected as a Foreign Associate of the Academie des Science (Paris) and became a council member of the Royal Society, and on 26 November 1701 he was elected as a Member of Parliament from Cambridge.

Newton’s interest in astronomy was heightened by his visit in 1704 to John Flamsteed, the Astronomer Royal, at Greenwich (1646–1716). It is during this period that Newton published his first edition of Opticks. On 16 April 1705 Newton was knighted by Queen Anne (1665–1714), who reigned from 1702 to 1714.

He was very productive from 1707 to 1711, publishing Arithmetica universalis, another edition of the Principia, De natura acidorum, Enumeratio, De quadratura Lexicon technicum and Analysis per quantitatum.

Newton maintained his correspondence with other eminent scientists of his era. In 1715 he began correspondence with Gottfried Leibniz (1646–1716), a German philosopher and
mathematician, which was curtailed because Leibniz died in 1716. During 1717–1722, Newton had numerous publications, including his Second Edition of Opticks (1719), first English edition of Universal Arithmetic (1720), the third English edition of Opticks, and second edition of Commercium epistolicum.

It was during 1722 (aged 81 years) that Newton experienced urinary stone problems, discussed in greater detail later. A third edition of Principia was published in 1726, but his health began to fail and Newton died on 20 March 1727, in Kensington, London.

NEWTON’S ACHIEVEMENTS

PHYSICS – ANALYSIS OF LIGHT

The core of Newton’s contribution was concerned with the physics of colour; an ancient theory extending back at least to Aristotle held that a certain class of ‘colour’ phenomena, e.g. the rainbow, arose from the modification of light, which appears white in its pristine form. Descartes had generalized this theory for all colours and translated it into mechanical imagery. Through a series of experiments in 1665 and 1666, in which the spectrum of a narrow beam was projected onto the wall of a darkened chamber, Newton denied the concept of modification and replaced it with that of analysis. Basically, he denied that light is simple and homogeneous, stating instead that it is complex and heterogeneous, and that the phenomena of colour arises from the separation of the heterogeneous mixture into its simple components. Newton’s concept of ‘Of Colours’ was published in Book One of Opticks, wherein he discarded the previous concepts of Aristotle and Descartes.

He held that individual rays (that is, particles of given size) excite sensations of individual colours when they strike the retina of the eye. He also concluded that rays refract at distinct angles; hence, the prismatic spectrum, a beam of heterogeneous rays, i.e. incident on one face of a prism, separated or analysed by the refraction into its component parts, and that phenomena such as the rainbow are produced by refractive analysis. Because he believed that chromatic aberration could never be eliminated from lenses, Newton developed the reflecting telescope, constructing the first. The heterogeneity of light has been the foundation of physical optics since his time [3].

ASTRONOMY

Newton originally applied the idea of attraction and repulsion solely to the range of terrestrial phenomena. In 1679, not long after he had embraced the concept, another application was suggested in a letter from Robert Hooke (1635–1703), who suggested that the force of gravity could be measured by using the motion of a pendulum (1666), and attempted to show that the Earth and Moon follow an elliptical path around the Sun. In 1672 Hooke discovered the phenomenon of diffraction (the bending of light rays around corners); to explain it, he offered the wave theory of light. He stated the inverse square law to describe planetary motions in 1678, a law that Newton later used in modified form. Hooke complained that he was not given sufficient credit for the law and became involved in bitter controversy with Newton [3].

Newton demonstrated the rotation of the Earth with an experiment where a body was dropped from a tower; as the tangential velocity at the top of the tower is greater than that at the foot he predicted the body should fall slightly to the east. He sketched the path of fall as part of a spiral ending at the centre of the earth. Nearly 5 years later, in August of 1684, Newton was visited by the British astronomer Edmond Halley, who was also troubled by the problem of orbital dynamics. Upon learning that Newton had solved the problem, Halley extracted Newton’s promise to send the demonstration and 3 months later received a short tract entitled De Motu (On Motion). In 2.5 years, the tract De Motu grew into Philosophiae Naturalis Principia Mathematica, which is not only Newton’s masterpiece but also a fundamental work for the whole of modern science.

Significantly, De Motu did not state the law of universal gravitation. For that matter, even though it was a treatise on planetary dynamics, it contained none of the three Newtonian laws of motion. Only when revising De Motu did Newton embrace the principle of inertia (the first law) and arrive at the second law of motion. The second law, the force law, proved to be a precise quantitative statement of the action of the forces between bodies, which had become the central members of his system of nature. By quantifying the concept of force, the second law completed the exact quantitative mechanics that has been the paradigm of natural science ever since.

The quantitative mechanics of the Principia is not to be confused with the mechanical philosophy. The latter was a philosophy of nature that attempted to explain natural phenomena by means of imagined mechanisms among invisible particles of matter. The mechanics of the Principia was an exact quantitative description of the motions of visible bodies. It rested on Newton’s three laws of motion: (i) that a body remains in its state of rest unless it is compelled to change by a force impressed on it; (ii) that the change of motion (the change of velocity times the mass of the body) is proportional to the force impressed; and (iii) that to every action there is an equal and opposite reaction. The analysis of circular motion in terms of these laws yielded a formula of the quantitative measure, in terms of a body’s velocity and mass, of the centripetal force necessary to divert a body from its rectilinear path into a given circle. When Newton substituted this formula into Kepler’s third law, he found that the centripetal force holding the planets in their given orbits about the Sun must decrease with the square of the planets’ distances from the Sun. Because the satellites of Jupiter also obey Kepler’s third law, an inverse-square centripetal force must also attract them to the centre of their orbits. Newton was able to show that a similar relation holds between the Earth and its Moon, with the help of the Newtonian telescope.

POLITICAL

MASTER OF THE MINT

In 1696 Newton was appointed warden of the mint; although he did not resign his Cambridge appointments until 1701, he moved to London and henceforth centred his life there. As warden and then Master of the Mint, Newton drew a large income, as much as £2000 per annum. Added to his personal estate, the income left him a rich man at his death. The position, regarded as a sinecure, was treated otherwise by Newton. During the great re-issue of coins, there was need for him to be actively in command; afterwards, however, he chose to exercise himself in the office. Above all, he was interested in counterfeiting. He became the terror of London counterfeiters, sending a goodly
number to the gallows and finding in them a socially acceptable target. On 26 November 1701 Newton was elected to Parliament by the Cambridge Senate.

INTEREST IN RELIGION AND THEOLOGY

Newton found time to explore other interests, such as religion and theology. In the early 1890s he had sent Locke a copy of a manuscript attempting to prove that Trinitarian passages in the Bible were latter-day corruptions of the original text. When Locke made moves to publish it, Newton withdrew in fear that his anti-Trinitarian views would become known. In his later years he devoted much time to interpreting the prophecies of Daniel and St. John, and to a closely related study of ancient chronology. Both works were published after his death [3].

NEWTON'S HEALTH PROBLEMS

Isaac Newton's physical and mental health were issues in his life from the moment he was born prematurely on 25 December 1642. His plight was further compromised when his mother abandoned him at 3 years old. Such early difficulties may have contributed to his mental ailments that troubled him later in his life.

Newton was seen in his adult life to manifest both bipolar and schizoid traits [5,6]. Some have suggested that he always had an 'uneasy' sense, as his father died before he was born and his mother abandoned him. From this it is construed that this sense of loneliness drove him to establish his intellectual superiority and notoriety through his work [6]. However, despite his cerebral genius, he had mental shortcomings as well. Even Samuel Pepys (1633–1703), the English diarist, and John Locke, both his friends, commented in 1692 that '... Newton's mind was deranged' [7].

There is a suggestion that this mental affliction was attributable to mercury poisoning from his chemical experiments. Indeed, Newton was known to experiment widely in his laboratory with mercury [7]. Mercury poisoning is associated with '... morbid irritability, insomnia, and mental hyperactivity' [8], all the features that Newton displayed throughout his life. Modern studies of Newton's hair at Cambridge University showed high levels of mercury [7]. Also, mercury poisoning is known to cause nephrotic syndrome [8]; did this occur to Newton?

However, mercury poisoning alone does not account for Newton's bipolar affect. He had evidence of hypomania and depression in his childhood (before his work with mercury), where he was known to be withdrawn, playing little with his peers. He also displayed significant bouts of energy by constructing complex mechanical devices and by painting the walls of his room [6]. In the years that followed at Cambridge, he was recalled as having few personal contacts. He was noted later in 1693 to suffer from considerable mood swings during a 2-week period, where he slept only 9 h.

He also suffered from significant paranoia, being unable to maintain long-term relationships. He continuously sought enemies and villains in his life, from Robert Hooke to the French Academicians. One acquaintance stated that Newton was '...the most fearful, cautious, and suspicious temper that I ever knew' [6].

From a urological perspective, Newton's life was plagued by urolithiasis and urinary incontinence. In August, 1724, the presence of a dreadful disease declared itself by his voiding without any pain, a stone, about the size of a pea, which passed in two pieces [4]. Possible evidence of his urolithiasis was seen in 1725, when an attack of gout forced him to step down from the Royal Society, suggesting that his stones may have been uric acid.

Newton's final years were marked with recurrent illnesses and deteriorating health. He was noted in this period to suffer from '... weakness of the sphincter, and incontinence' [10]. On 4 March 1727 he experienced severe pain, which was diagnosed as a stone in the bladder for which his physician offered '... no hope of recovery. His pain was so severe that it was described that '... the pain rose to such a height that the bed under him, and the very room shook with his agony, to the wonder of those that were present' [10].

CONFLICT OF INTEREST

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Correspondence: Gilbert J. Wise, The Division of Urology, Maimonides Medical Center, Brooklyn, New York 11219, USA. e-mail: gwise@maimonidesmed.org
Re-evaluation of the Tumour-Node-Metastasis staging of locally advanced renal cortical tumours: absolute size (T2) is more significant than renal capsular invasion (T3a)

ALANA M. MURPHY, SCOTT M. GILBERT, AARON E. KATZ, ERIK T. GOLUBOFF, IHOR S. SAWCZUK*, CARL A. OLSSON, MITCHELL C. BENSON and JAMES M. MCKIERNAN
Departments of Urology, Columbia University Medical Center, New York, NY and *Hackensack University Medical Center, Hackensack, NJ, USA

OBJECTIVE
To determine which factor was more predictive of adverse outcome in our institutional experience with T2N0M0 and T3aN0M0 renal cortical tumours (RCTs) treated surgically, as the current Tumour-Node-Metastasis (TNM) staging system for RCTs differentiates between tumours of >7.0 cm but confined to the renal capsule (T2) and tumours that extend through the renal capsule regardless of size (T3a).

RESULTS
In all, 717 patients had a partial or radical nephrectomy for RCT during the study period. After exclusion criteria were applied, 21 patients with T2N0M0 and 97 with T3aN0M0 tumours were eligible; the median (mean, range) age was 63 (16.6–88.3) years and follow-up 30.5 (40.8, 6–162) months. The estimated 5-year disease-free survival was 68% and 85% for T2N0M0 and T3aN0M0 RCT, respectively ($P=0.002$). The 5-year disease-specific survival was 81% and 94% for the T2N0M0 and T3aN0M0 groups, respectively ($P=0.085$).

CONCLUSION
Patients with T3aN0M0 tumours appear to have better disease-free and disease-specific survival than those with T2N0M0 disease, which suggests that tumour invasion through the renal capsule is not as significant as the absolute tumour size.

MATERIALS AND METHODS
We analysed our institutional database of surgical urological oncology for all patients with T2N0M0 and T3aN0M0 RCT treated with partial or radical nephrectomy from 1988 to 2002. All patients with preoperative metastasis, bilateral or multifocal tumours, nonsporadic disease or benign histology were excluded from analysis. A follow-up of ≥6 months from the time of surgery was required for inclusion. Primary outcomes included local and distant recurrence, and death.

OBJECTIVE
To determine which factor was more predictive of adverse outcome in our institutional experience with T2N0M0 and T3aN0M0 renal cortical tumours (RCTs) treated surgically, as the current Tumour-Node-Metastasis (TNM) staging system for RCTs differentiates between tumours of >7.0 cm but confined to the renal capsule (T2) and tumours that extend through the renal capsule regardless of size (T3a).

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CONCLUSION
Patients with T3aN0M0 tumours appear to have better disease-free and disease-specific survival than those with T2N0M0 disease, which suggests that tumour invasion through the renal capsule is not as significant as the absolute tumour size.
examined the prognostic validity of the kidney. Although recent studies have shown that a small tumour invasion into the perirenal fat was associated with adverse outcome, we reviewed our institution’s experience with patients treated surgically for T2N0M0 and T3aN0M0 RCT.

INTRODUCTION

The purpose of cancer staging systems is to predict a patient’s prognosis based on clinical and pathological findings. An accurate cancer staging system is extremely valuable for many reasons. With accurate prognostic information, a physician is able to determine suitable treatment options, effectively counsel patients about various treatments and develop an appropriate surveillance scheme after treatment. Physicians rely on cancer staging systems as integral tools in patient care; the ability of a staging system to accurately reflect clinical outcomes is paramount.

The American Joint Commission on Cancer (AJCC) TNM staging system for renal cortical tumours (RCTs) was last modified in 2002, and is based on gross tumour characteristics such as size, local extent, vascular invasion, nodal involvement and presence of metastatic disease [1]. In 1997, the TNM staging system was revised, resulting in a change in the T2N0M0 classification from tumours confined to the kidney and >2.5 cm, to those confined to the kidney and >7.0 cm [2]. The classification of T3aN0M0 RCT has been in place since 1978, when the AJCC TNM staging system was first created. The T3aN0M0 staging classification is defined as a tumour that extends through the renal capsule and into perinephric tissue, but not beyond Gerota’s fascia, independent of size. Tumours were also classified based on histological subtype and Fuhrman nuclear grade.

Exclusion criteria included bilateral tumours, multifocal disease, benign histology, non-spuradic RCC, positive surgical margin on final pathology, and presence of nodal involvement or distant metastatic disease. Patients were followed after surgery with physical examinations, chest radiographs and abdominal and pelvic CT. A follow-up of ≥6 months was required for inclusion in the analysis, with follow-up defined as the time from nephrectomy to the date of death or the date of last contact. Survival was analysed using the Kaplan-Meier method, with the log-rank test used with \( \alpha = 0.05 \) to determine the statistical significance between T2N0M0 and T3aN0M0 stages for disease-free or disease-specific survival. Survival was also analysed on the basis of Fuhrman grade and tumour size.

RESULTS

In all, 717 patients had a radical or partial nephrectomy for renal masses at our institution between 1988 and 2002. Patients with benign histology (75), no available tumour stage (20), T1 (298), T3b (87), T3c (10) and T4 tumours (11) were excluded from the analysis. In all, 43 patients had a T2 and 173 a T3a tumour. Patients with preoperative metastasis (22), bilateral tumours (16) or multifocal disease (20) were also excluded from the analysis. An additional 40 patients were excluded as they had insufficient follow-up. After the exclusion criteria were applied, 21 patients with T2N0M0 and 97 with T3aN0M0 RCT were included in the dataset for analysis; the clinical and pathological characteristics are shown in Table 1. There was no statistically significant difference (\( P > 0.05 \)) between the T2N0M0 and T3aN0M0 groups on the basis of age, sex, surgical technique, histology and Fuhrman grade. Because the T2N0M0 and T3aN0M0 groups were well-matched, observed differences in recurrence and survival rates are more probably explained by tumour stage.

The median follow-up was similar in the two groups (Table 1). At the time of analysis, seven T2N0M0 patients (33%) had had a recurrence; one developed a local recurrence, five metastatic disease and one had both. In the T3aN0M0 group, six patients (6%) had disease recurrence, all with distant metastases. In the T2N0M0 group, 13 (62%) had no evidence of disease, four (19%) were alive with disease, three (14%) were dead from RCC and one (5%) from an unknown cause; in the T3aN0M0 group, the respective values were 84 (87%), two (2%) and four (4%), with three (3%) dead from an unrelated cause and four (4%) from an unknown cause.

The estimated 5-year disease-free and disease-specific survival for the two groups are shown in Fig. 1a,b; survival analysis using Fuhrman grade showed that it was a significant predictor of disease-free survival (\( P = 0.028 \); Fig. 1c). When tumour size was used as a categorical variable for survival analysis, a threshold of 8.0 cm was a statistically significant predictor of disease-free survival (\( P = 0.015 \)). When analysed as a continuous variable with Cox regression analysis, tumour size was almost significant as a predictor of disease-free survival (\( P = 0.076 \)).

DISCUSSION

Since its inception, the AJCC TNM staging system has been the most widely used predictor of kidney cancer recurrence and mortality. Given its pivotal role in guiding treatment and surveillance after surgery, the accuracy of the staging system should be periodically reviewed. Although an ideal prognostic model would incorporate all factors known to be predictive of clinical outcome, we have shown that tumour size is an important predictor of survival. This finding is consistent with previous studies that have shown a correlation between tumour size and survival. The prognostic value of tumour size has been confirmed in various studies, including those by the AJCC, the University of California at Los Angeles (UCLA) and others. These studies have demonstrated that tumour size is a significant predictor of recurrence and survival rates.

In conclusion, this study has shown that tumour size is an important predictor of survival in patients with RCTs. The prognostic validity of the T2N0M0 and T3aN0M0 classifications needs to be periodically reviewed, as it may change with advances in treatment and follow-up techniques. This study has added to the growing body of evidence that tumour size is a critical factor in determining patient outcome. Further studies are needed to determine the best approach to the management of patients with RCTs based on tumour size, as this may have implications for treatment and follow-up.
outcome, a comprehensive model is difficult to achieve. Furthermore, as prognostic models become more inclusive and complex, they may become more difficult to use by clinicians. In an effort to improve a practical tool, we chose to work within the framework of the TNM classification system and examine the ability of the T2N0M0 and T3aN0M0 classifications to accurately predict the clinical course of RCC in a modern patient cohort.

There has been debate about the current T2N0M0 and T3aN0M0 classifications for RCC. Levy et al. [6] examined the clinical course of 286 patients with RCTs who had a nephrectomy. Patients with T2N0M0 and T3aN0M0 disease had an equivalent rate of postoperative metastasis and time to development of metastasis. About 27% of patients with T2N0M0 cancer and 30% with T3aN0M0 disease developed metastasis, both with a median time to diagnosis of 32 months. The distinction between lower and higher stages was more pronounced, with 7% of T1 patients and 49% of T3b developing metastasis. More recently, the Memorial Sloan Kettering Cancer Center group reviewed their experience with RCC and developed a postoperative prognostic nomogram [7]. Interestingly, stage T2N0M0 tumours were assigned a greater point value than T3aN0M0 tumours in this nomogram, corresponding to a worse predicted clinical outcome for the T2N0M0 group.

Based on our institution’s experience with surgically managed clinically localized RCTs, the current T2N0M0 and T3aN0M0 classification does not accurately predict disease recurrence and death. Indeed, the current classification inversely correlates with risk of recurrence and death. In the 2002 TNM staging system, it is implied that on average, patients with T2N0M0 disease should have a more favourable prognosis and a better chance of cure than those with T3aN0M0 disease. In contrast to this model, the present T2N0M0 patients had a worse clinical course than the T3aN0M0 patients. The 5-year disease-free survival was 68% in the T2N0M0 and 85% in the T3aN0M0 group, and the T2N0M0 patients failed sooner after surgery than the T3aN0M0 patients (P = 0.002). The 5-year disease-specific survival was 81% and 94% in the T2N0M0 and T3aN0M0 groups, respectively (P = 0.085). Although the difference in disease-specific survival was not quite significant, the discrepancy between disease-free and disease-specific survival

FIG. 1. Kaplan-Meier survival curves. a, the disease-free curves for patients with T2N0M0 (green) and T3aN0M0 (red) RCC; the 5-year disease-free survival was 68% (mean 66 months, 95% CI 39–93) in the T2N0M0 and 85% (mean 139 months, 95% CI 123–154) in the T3aN0M0 group (P = 0.002); b, the disease-specific curves for patients with T2N0M0 (green) and T3aN0M0 (red) RCC. The 5-year survival was 81% (mean 96 months, 95% CI 78–113) in the T2N0M0 and 94% (mean 149 months, 95% CI 136–162) in the T3aN0M0 group (P = 0.085); c, disease-free curves stratified by Fuhrman grade (1, red; 2, green; 3, light red; 4, light green) for 109 patients with T2N0M0 or T3aN0M0 RCC (P = 0.028).

<table>
<thead>
<tr>
<th>TABLE 1 Characteristics of patients with T2N0M0 and T3aN0M0 RCC</th>
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<tr>
<td>Characteristic</td>
</tr>
<tr>
<td>No. of patients</td>
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<tr>
<td>Median (range) age, years</td>
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<tr>
<td>Sex, n (%)</td>
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<td>Surgical technique, n (%)</td>
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<tr>
<td>Histology, n (%)</td>
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<td>Chromophobe</td>
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<td>Fuhrman grade</td>
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<td>2</td>
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<td>3</td>
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<td>4</td>
</tr>
<tr>
<td>Unclassified</td>
</tr>
<tr>
<td>Median (range): size, cm</td>
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<tr>
<td>follow-up, months</td>
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*two-tailed t-test; †chi-square test.
suggests that currently, the T2N0M0 and T3aN0M0 classifications do not accurately reflect prognosis.

Similar to previously published studies, our analysis showed the prognostic value of Fuhrman grade in predicting clinical outcome [8,9]. When analysing survival based on tumour size alone, we determined that comparing tumours of ≤8.0 cm in greatest dimension to those ≥8.0 cm gave a significant difference in disease-free survival (P = 0.015). When tumour size was analysed as a continuous variable using Cox regression analysis, tumour size was almost significant as a predictor of disease-free survival.

Although renal capsular invasion is routinely assessed during pathological examination of a nephrectomy specimen, the classification of renal capsular invasion has been questioned [10]. The presence of renal capsular invasion is often difficult to determine accurately and no definitive pathological criteria have been established to aid in this decision process. In this respect, the classification of renal capsular invasion may not be a reliable prognostic variable. The questionable nature of renal capsular invasion status combined with the prognostic value of tumour size suggests that a reclassification of the TNM system relying more on absolute tumour size may be useful.

Our direct comparison of T2N0M0 and T3aN0M0 survival suggests that revision of the current RCT staging system is warranted. As shown by the present analysis, renal capsular invasion did not correlate with a worse prognosis than a larger tumour confined to the kidney. The study has several limitations. The analysis was based on one institution’s experience with patients treated surgically for T2N0M0 and T3aN0M0 RCT and subsequently, the final dataset may be limited by its small size and potential lack of power. However, these findings might be confirmed with further analysis at other institutions with a considerable experience in the surgical management of RCC. Despite the inherent limitations of the study, we think that the findings warrant further consideration and reassessment of the accuracy of the T2N0M0 and T3aN0M0 classification in a larger study.

Our findings indicate that further examination of the T2N0M0 and T3aN0M0 classification, as defined by the 2002 AJCC TNM staging system for RCT, is warranted. Collaboration with other institutions would increase the power of the analysis and a more definitive trend may be detected. We conclude that formulating a definitive modification to the RCT staging system accounting for the superior predictive value of absolute size over renal capsular invasion would merit consideration during the next AJCC revision of the TNM classifications.

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CONFLICT OF INTEREST

None declared.

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Correspondence: James M. McKiernan, Columbia University Medical Center, Department of Urology, 161 Fort Washington Ave 11th Floor, New York, NY 10032, USA. e-mail: jmm23@columbia.edu

Abbreviations: AJCC, American Joint Commission on Cancer; RCT, renal cortical tumour.
The prevalence of renal cell carcinoma diagnosed at autopsy

STEVEN R. MINDRUP, JESSICA S. PIERRE, LAILA DAHMOUSH* and BADRINATH R. KONETY†
Departments of Urology, *Pathology and †Epidemiology, University of Iowa, Iowa City, IA, USA

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INTRODUCTION

Tumours of the kidney and renal pelvis account for 3% of all new cancer diagnoses and 3% of cancer deaths. The are an estimated 35 710 new cases of renal cancer diagnosed in 2004, with an estimated 12 480 resulting deaths. Survival rates have increased from 56% in 1983–85 to 62% in 1992–97 [1]. Current reports show an increasing incidence of renal cancer. Several earlier series postulated this increasing incidence to be a result of more widespread and aggressive imaging techniques [2–4], but more recent series have confirmed that the incidence at all stages has increased [5]. In an analysis of the Surveillance, Epidemiology and End Results database, Hock et al. [6] confirmed that the incidence of localized, regional, and distant metastatic renal cancer had increased over the last 20 years. Some authors have called for a re-evaluation of incidence data, to refute or support these observations [7]. We sought to address this issue by comparing the incidence of occult renal cancer diagnosed at autopsy to the incidence of clinically diagnosed RCC during life over two periods separated by 30 years. The hypothesis was that if the observed increase in the incidence of asymptomatic RCC was a result of the widespread use of sophisticated imaging techniques, the rate of occult RCC detected only at autopsy should be declining, as most renal tumours would more likely be detected during a patient’s lifetime. Conversely, if there was a true increase in the incidence of RCC between these periods, the rate of detection only at autopsy would be unchanged or increase.

OBJECTIVE

To compare the rate of renal cell carcinoma (RCC) detected only at autopsy, from two periods, to determine if the apparent recent increase in RCC in the USA is a true increase or mainly a result of improved imaging techniques, as a true increase in the clinical incidence of RCC should not affect the number of previously undiscovered RCC found only at autopsy.

RESULTS

Between 1955–60 and 1991–2001 there was a 55% reduction in the mean annual number of autopsies. The proportion of malignant renal masses (RCC) did not change significantly (35.4% to 32.8%). The rate of previously unsuspected RCC detected only at autopsy did not change significantly (0.91 vs 0.72 per 100 autopsies).

CONCLUSION

The number of renal masses, both benign and malignant, discovered only at autopsy is declining, possibly because of better detection before death. However, the rate of occult kidney cancer per 100 autopsies did not change significantly between the two periods, suggesting a true increase in the frequency of clinically detected kidney cancer.

KEYWORDS

carcinoma, renal cell, incidence, diagnosis, autopsy

PATIENTS AND METHODS

We identified all individuals who underwent autopsy in two periods, 1955–60 (3307) and 1991–2001 (2938), and who were identified with renal tumour either before or after death. Information was obtained on age, sex, histological type and size of tumour, and whether the tumour was identified before or only after death. All cases of RCC detected at autopsy were reviewed for this analysis by one pathologist (L.D.).

All cases of RCC detected at autopsy were evaluated and inspected grossly for visible lesions. All observed lesions were step-sectioned. In kidneys with no lesions, or if the patient had no history suggestive of renal disease, a representative transverse section of tissue encompassing the cortex, medulla and renal pelvis is submitted for histological examination. All autopsy reports were reviewed by two authors (J.S.P. and B.R.K.) and information extracted on age, sex, histological type and size of tumour, and if the tumour was clinically identified before death or at autopsy only. Data on the incidence of clinically identified RCC at our institution during the corresponding periods were obtained from the University of Iowa institutional cancer registry. All of the slides of the original haematoxylin and eosin-stained sections of the kidneys from all of the autopsy specimens reported to have RCC or adenoma were reviewed again by one pathologist (L.D.). Tumour size, Fuhrman grade and histological subtype of RCC were assessed. All cases of occult RCC were identified and confirmed through the pathological review. Student’s t-test and a chi-square test were used to compare tumour size, tumour histological subtype distribution.
and rate of occult RCC per 100 autopsies between the periods.

RESULTS

From 1955–60 to 1991–2001 there was a 55% reduction in the average annual number of autopsies (Table 1). There were 14 renal masses, including 10 RCC that had been diagnosed before death and found at autopsy in the group from 1955–60. The remainder were (one each) adenoma, fibroma, Wilms’ tumour and fibrosarcoma. There were seven renal masses, all of which were RCC diagnosed before death and documented as being present at autopsy in the group from 1991–2001. The distribution of the histological type of occult renal masses detected at autopsy is shown in Table 2. Most of them tended to be RCC, adenoma or fibroma. The distribution of the histological subtype of RCC among the previously known or occult cancers detected only at autopsy is also shown in Table 2. Among the occult RCC in the 1955–60 group, conventional clear cell RCC predominated (71%), while papillary RCC was predominant in the more recent group of patients (62.5%). Of the papillary tumours, two of five from 1955–60 and three of 11 from 1991–2000 were multifocal. The mean size of the occult RCC detected at autopsy was also 65% less in the more recent group, but this difference was not statistically significant.

The pathological diagnoses of renal cell cancers has changed over the years; we had all slides from both groups reviewed by one pathologist and re-graded according to the system currently in use [8]. In the 1955–60 group, 15 diagnoses were changed from tubular or cortical adenoma to papillary, clear cell or chromophobe RCC; in the 1991–2001 group only three diagnoses were changed. The proportion of occult renal masses that were RCC did not change significantly (35.4% to 32.8%) between the periods. In addition, the rate of occult RCC detected only at autopsy did not change significantly between the periods (0.91 vs 0.72 per 100 autopsies).

DISCUSSION

The size of occult renal tumours detected at autopsy is decreasing; with the increasing use of sophisticated imaging techniques, the size of tumours escaping clinical detection is also decreasing. Recent reported studies suggested an increased incidence of RCC [5,6]. The potential lethality of these smaller tumours is unclear, especially in older individuals. There also appears to be a change in the distribution of histological subtypes among the occult RCC between these periods, 30 years apart. The distribution of histological subtypes of RCC among the discovered and occult tumours was also relatively stable over the two periods (Table 2). The difference in the size of the occult tumours detected during the two periods is decreasing, although the difference was not statistically significant. Although the occult tumours detected in 1991–2001 were smaller, they are still deemed to be clinically significant RCC by the
PREVALENCE OF RCC DIAGNOSED AT AUTOPSY

pathological size criterion that separates papillary adenoma from carcinoma with a threshold of 0.5 cm.

Wunderlich et al. [9] reviewed 23,247 autopsies from two institutions over one decade and found the incidence of RCC detected at autopsy to be increasing. However, the determination of RCC was based on the autopsy report. This can sometimes be incorrect and several tumours classified as adenomas previously would now qualify as RCC. In the present series of autopsies from 1955–60 there were 18 tumours that were originally classified as adenomas that were reclassified as RCC. Using the original classification as given in the autopsy report would have lead to an underestimate of the incidence in the reference period from 30 years ago and erroneously show an increased incidence in occult RCC. In a series of 7970 autopsies examining the histological types of tumours found incidentally and those found clinically, the incidental tumours typically tended to be of less malignant potential [10]. The clinical presentation of renal tumours has been the focus of other autopsy series. Hellsten et al. [11] reported 350 cases of RCC after reviewing 16,294 autopsies, and concluded that most patients died with their renal tumour rather than from it. Similarly, Hajdu and Thomas [12] reported 100 cases of RCC found after reviewing 15,570 autopsies between 1935 and 1964, and focused mainly on the clinical characteristics of the tumour and metastatic rate as it related to size. The present series differs from these, as it is the only series to our knowledge to compare two distinctly different and chronologically separate periods. In addition, the inter-observer variability that can plague longitudinal pathological studies was eliminated by having one pathologist review all cases of renal masses from both periods.

Occult RCC detected at autopsy only constitutes a small proportion of all reported cases of RCC, and the rate of unsuspected RCC detected at autopsy, as calculated by the number of previously unsuspected RCC per 100 autopsies, has remained stable (0.91 vs 0.72). If the increasing incidence were strictly a result of the increased use of imaging, fewer tumours should be discovered only at autopsy, concomitant with the increased clinical incidence. However, this does not appear to be the case, at least in our institution. We cannot be certain that this is representative of a more population-based sample, but if the data are representative, the nationally observed increasing incidence of RCC represents a true rise in the occurrence of these tumours and is not merely an artefactual increase resulting from the more aggressive use of radiological investigations.

While the more widespread and ready use of imaging techniques could certainly contribute to the increased incidence, the data presented here imply that other factors might be involved. Some of the potential factors include an increase in the elderly population, environmental (e.g. cadmium exposure), lifestyle changes (increased incidence of smoking) and dietary factors.

There are some inherent limitations to the present study; it was not population-based and although the patients at our academic medical centre can be considered fairly representative of other similar centres, it is unclear if these data mirror those of a nationally representative sample. Unfortunately there is currently no easy source of population-based data that would permit such an analysis. A sampling bias could not be excluded, as fewer patients agreed to an autopsy in the more recent period, and the true denominator (i.e. patients’ families offered autopsy who declined) is unclear. There could also be differences in tissue sampling at the time of autopsy, as only grossly visible lesions were sectioned and analysed. There has also been a change in the nomenclature of some renal tumours, which is reflected in the present data.

The number of cases of renal cancer diagnosed only at autopsy has remained stable over the last 40 years, despite the use of more aggressive and sophisticated imaging techniques. This suggests a true increase in the incidence of RCC; the increasing incidence of RCC presents important healthcare implications for patients and physicians, requiring that we seek potential explanations through future research.

CONFLICT OF INTEREST

None declared.

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Correspondence: Badrinath R. Konety, Department of Urology, University of Iowa, 200 Hawkins Drive, 3 RCP, Iowa City, IA 52242–1089, USA.

e-mail: badrinath-konety@uiowa.edu
Radical prostatectomy: pathology findings in 1001 cases compared with other major series and over time

SIMON R.J. BOTT, A. ALEX FREEMAN*, SALLY STENNING†, JONATHAN COHEN, M. CONSTANCE PARKINSON* and THE UROLOGISTS AND PATHOLOGISTS CONTRIBUTING TO THE DATABASE

Institute of Urology, University College London, *UCL Hospitals Trust, and †MRC Clinical Trials Unit, London, UK

SM Bhanot, PJR Boyd, C Colville, M Emberton, RS Kirby, EPN O'Donoghue, PIR Shah, P Shridhar, A Winstanley, MPA Young

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OBJECTIVE

To examine the preoperative features and pathological outcomes of clinical significance of 1001 consecutive essentially unscreened men who had a radical prostatectomy (RP) in the UK between 1988 and 2002, and their changes over time.

PATIENTS AND METHODS

The details of men whose RP specimen was submitted for analysis were entered into the RP database held at the University College Hospital, London; the National Health Service and private patients of 17 surgeons were included. The age, mode of diagnosis, preoperative prostate specific antigen (PSA) level, biopsy and RP findings were compared over time.

INTRODUCTION

Radical prostatectomy (RP) findings may be expected to differ among countries, reflecting ethnicity and the presence/absence of PSA screening and surgical experience. Numerous major RP series giving both findings and follow-up are available from the USA, Europe and Australia [1-7] but the results from a large single UK practice are not available. Thus we report a continuous UK series, examined by one pathologist, from which it is possible to assess changes over time.

RESULTS

The mean (range) age of the men was 62 (40–76) years, the median PSA 8 (0.1–146) ng/mL and the median biopsy Gleason sum score 6; these preoperative features did not change over the study period. The diagnosis of prostate cancer was made by transurethral resection of the prostate alone in 48 men (5%). The maximum number of patients receiving neoadjuvant androgen ablation was 21 (33%) in 1996, and subsequently declined. The median (range) RP Gleason sum score was 7 (4–9). The biopsy Gleason score correlated with the prostatectomy Gleason score in 252 (47%) of 536 men, being lower in 170 (32%) and higher in 113 (21%). The median tumour volume was 2 mL (focus of invasive acini – 31 mL) and the incidence of positive intra- and extraprostatic margins was 52%. Both tumour volume and extraprostatic margin positivity declined with time.

CONCLUSIONS

The preoperative features and pathological findings from this UK series are similar to those of other reported cohorts from unscreened populations. The incidence of positive extraprostatic surgical margins, tumour volume and stage decreased with time.

KEYWORDS

prostate cancer, radical prostatectomy, pathological outcome, surgical margin, stage, biopsy
radical prostatectomy pathology findings

The pathological stage was reported according to the 1997 system [13]. The pT category was used for tumours with an intraprostatic positive limit and no evidence of spread beyond the gland in any other section. Stage pT3b was recorded when carcinoma infiltrated the muscle of the prostate but not reaching the inked surgical limit were categorized as specimen-confined. A circumferential positive margin was recorded as intraprostatic when the resection line transected the prostate gland at a point including carcinoma, and extraprostatic in a gland removed with periprostatic adipose tissue infiltrated by tumour which the resection line transected.

The statistical tests were used to seek evidence of a general upward or downward trend in results over the period assessed. Data in categories were evaluated using the chi-square test for trend applied to the categories. For continuous, approximately normally distributed data, an ANOVA for more than two groups was used. The percentage agreement between biopsy and RP Gleason score increased with the number of cores submitted (37% agreement in a single core. Tumours diagnosed solely on biopsy were identified only on biopsy (Table 2).

In Table 1 the biopsy Gleason sum score is grouped into predefined categories and a chi-square test for trend applied to the categories. For continuous, approximately normally (symmetrically) distributed data, an ANOVA with a test for linear trend was used. The mean (range) age at RP was 62 (40–76) years and did not change significantly over time (test for linear trend, \( P = 0.77 \)). The preoperative median PSA (951 men) was 8 (0.1–146) ng/mL; this did not change significantly throughout the 13 years of the study (test for linear trend, \( P = 0.15 \)). From the early 1990s biopsy rapidly replaced TURP as the mode of diagnosis. During 1988–91, 51% of men were diagnosed on prostatic biopsy alone, compared with 96% during 2001. In the entire series the diagnosis was made only on TURP findings in 48 (5%) of the 948 patients.

In all, 118 patients had preoperative androgen ablation, of whom 89 (75%) were treated between 1996 and 2000. In a further 24 patients, radical surgery followed PSA relapse after radical radiotherapy. Nine patients received both androgen ablation and radiotherapy before surgery.

There were 628 patients whose prostatic cores were examined in the UCLH laboratory and in whom a radical Gleason score was not precluded by previous therapy. The median number of cores examined throughout the study was six; this increased from four in 1988–91 to seven in 2001, although the number of cores containing tumour remained the same. The median Gleason sum score in the 536 sets of core biopsies examined was 6 and did not change over time. The median (range) Gleason sum score in the RP specimen was 7 (4–9).

In Table 1 the biopsy Gleason sum score is compared with the Gleason score of the RP specimen; these were identical in 252/536 (47%), the biopsy score being lower and higher than the RP score in 170 (32%) and 113 (21%), respectively. Within the 536 patients the highest biopsy Gleason score equalled the RP score \((\leq 1)\) in 487 (91%) patients.

The percentage agreement between biopsy and RP Gleason score increased with the number of cores submitted (37% agreement with 5 five cores, 48% with six cores, 56% with 7 seven cores, \( P = 0.006 \)). There was no clear association between the level of agreement and number of positive cores, longest length invaded or percentage invaded in a single core. Tumours diagnosed solely on TURP had lower Gleason scores than those identified only on biopsy (Table 2).

### Table 1

<table>
<thead>
<tr>
<th>Gleason sum score</th>
<th>Biopsy, n (%)</th>
<th>TURP only, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤6</td>
<td>286 (54.6)</td>
<td>16 (80)</td>
</tr>
<tr>
<td>7</td>
<td>173 (33.0)</td>
<td>3 (15)</td>
</tr>
<tr>
<td>≥8</td>
<td>65 (12.4)</td>
<td>1 (5)</td>
</tr>
<tr>
<td><strong>RP</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤6</td>
<td>311 (36.9)</td>
<td>28 (58)</td>
</tr>
<tr>
<td>7</td>
<td>451 (53.6)</td>
<td>14 (29)</td>
</tr>
<tr>
<td>≥8</td>
<td>80 (9.5)</td>
<td>6 (13)</td>
</tr>
</tbody>
</table>

### Table 2

<table>
<thead>
<tr>
<th>Gleason sum score</th>
<th>Biopsy, n (%)</th>
<th>TURP only, n (%)</th>
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<tbody>
<tr>
<td><strong>Comparison of biopsy and RP specimen Gleason sum score</strong></td>
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<tr>
<td><strong>Method of diagnosis</strong></td>
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<tr>
<td>(biopsy or TURP alone)</td>
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<td><strong>Gleason score</strong></td>
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The median tumour volume was 2 mL, ranging from small foci of invasive acini to 31 mL. There was a small but statistically significant decline in volume over time ($P < 0.001$). The proportion of patients with larger volume tumours reduced substantially.

The pathological tumour stage and changes over time are shown in Fig. 1. Margin status according to site and number, and their changes over time, were available in 967 men (Table 3). The percentage of men with negative circumferential margins and gland-confined tumours increased significantly over time ($P = 0.002$) and the percentage of specimens in which the circumferential extraprostatic limit was involved decreased significantly ($P = 0.001$). There was no change in the incidence of positive intraprostatic margins or apical limits throughout the 13-year period. The surgical approach (retropubic vs perineal) was not recorded; only one urologist used perineal RP, and the site and number of the positive margins did not differ significantly from those of his colleagues.

Frozen sections were taken of the obturator lymph node in 75 patients, of whom 74 had surgery between 1988 and 1996. The results of the early frozen-section diagnosis yielded a false-negative rate of 33% and were published in detail elsewhere [8]. Metastatic carcinoma was seen in paraffin sections from the entire series in 24/856 (2.8%) cases.

**DISCUSSION**

There was no difference in terms of preoperative selection and pathological outcome between the NHS and private sectors. It was predicted that serum PSA incorporated in the ‘well-man screen’ offered by the private health insurers might give private patients an advantage for the detection of lower stage disease in a country with no national prostate cancer screening programme. Data on the numbers of PSA-detected cancers ($pT1c$) are not presented for patients in either sector, and a proportion of asymptomatic NHS and private patients may have requested a serum PSA test. Moreover, the influence of private/NHS status can only be accurately quantified if details of the entire population with prostate cancer in both sectors and who presented to the database urologists are known.

In the present series the age and age range at surgery was similar to that from other centres [4–6], and lower than the 65 years reported in the American/European multicentre study [15], but higher than the average age of 58.2 years in the John Hopkins series [16]. Direct comparison of preoperative PSA levels in the present series with that of other published reports is limited by the heterogeneity of assays used and the number of laboratories contributing. The mean of 10.7 ng/mL compares with 11.8 and 13 ng/mL [4,7] and the median of 8 ng/mL with 6.8 and 9 ng/mL [4,5], respectively.

In other publications [15,16] the percentage of men with a PSA level of $\leq 4$ ng/mL was much higher over a similar period (199% and 20%) than the 10% in the current series. In contrast, the proportion of patients with a PSA level of 10.1–20 ng/mL and $>20$ ng/mL is higher in the present series than in others [16].

Reflecting the introduction of PSA testing from 1989, and the fewer TURPs, the diagnosis of prostate cancer on TURP tissue decreased over the study period and accounted for 5% of all cases. A similar change from TURP to biopsy diagnosis was reported in the USA after 1989 [17], where TURP diagnosis was reported in 6–9% of cases [4,5,16,18]. Latterly, patients diagnosed with cancer incidentally on TURP frequently had peripheral zone biopsies taken to assess tumour extent.

The mode of tissue diagnosis is relevant to findings in the RP specimen. Tumours diagnosed on TURP are more likely to represent transition zone cancer, which is commonly of lower Gleason score than
peripheral zone tumours. The relationship between low radical Gleason score and TURP diagnosis was noted previously [5] and is supported by the current series (Table 2).

Pre-operative androgen ablation reduces the incidence of positive margins and extracapsular disease after RP [19,20]. When these findings were reported the proportion of men in the present series receiving androgen ablation was at its highest. More recently, series with a longer follow-up have reported no benefit in terms of overall survival [21,22]. The use of these agents in the UCLH series mirrored these findings and declined in the later years. Between 1988 and 2002, 33 patients had salvage RP, having developed PSA recurrence after radical radiotherapy. Only a few patients were offered or opted for surgery after radiotherapy failure, because of the increased risk of surgical complications.

The median Gleason sum score on the 536 core biopsies was 6, similar to that reported previously [4,7]. Only 2.8% of patients had a biopsy Gleason score of ≤4, in contrast with other series, in which low-grade disease comprised 10.5–14.3% of the population treated by radical surgery [4,5,7,23]. This may be explained by the derivation of preoperative Gleason scores from both TURP and core biopsies [4,5,7].

Comparison of the highest Gleason score on core biopsies and RP specimen showed an exact overall agreement of 47%. The agreement did not correlate with the area of tumour available for examination (reflected in the number of positive cores, length and percentage of core invaded). These findings are similar to those in other publications [24–26] but contrast with others, in which differences in score and biopsy tumour area were inversely related [27]. There was an increase in agreement over time (P = 0.01).

In previous reports the exact agreement on core biopsy and radical Gleason scores was 30–68% [25,26,28]; this increased to 72–97% if discrepancies of no more than one grade were included [24–26,28]. In many studies all the cases were reviewed during the project; by contrast, in the present series, the comparable values of 47% (exact agreement) and 91% (agreement ± one grade) reflect data generated during daily diagnostic reporting. Most publications agree that the correlation between biopsy and RP score is highest for biopsy scores of ≥7 (89% in the UCLH series) and in practices where biopsies are reviewed by several pathologists.

There is general agreement that the quantity of cancer at RP correlates with prognosis, some series reporting that tumour volume is an independent predictor of relapse [29,30], while others did not [7,31]. RP cancer volumes in the present series decreased over time, partly because of the decline in high-volume disease. In other series PSA screening and the increase in stage T1c cancers may account for the decrease in cancer volume over time [32].

Concern has been expressed that more small cancers may be detected by PSA screening, resulting in radical surgery for ‘insignificant’ cancer (≤0.2 to ≤0.5 mL and Gleason ≤6, respectively [32,33]). In the present series, only nine microscopic cancers were too small to measure at RP and these were distributed throughout the study years. There has been an increase in the proportion of insignificant tumours over time, but like other European and American series [17,34,35], this was not significant (P = 0.08).

The TNM classification [13] does not incorporate information on intra- or extraprostatic positive margin status. Positive margins may partly depend on different laboratory examination techniques and varying interpretative definitions used by pathologists. Of the RP samples in the current series, 43% were organ-confined (≤pT2b); this is higher than both the 29% [2] in patients undergoing surgery between 1977 and 1994, and the earlier series from Johns Hopkins, including surgery between 1982 and 1991, in which 37% and 36%, respectively, of patients had organ-confined disease [1,23].

The multi-institutional study of 2758 patients treated between 1970 and 1993 found pT2 cancer in 49% of the RP specimens [15]; in other series within 1982–98, 50–74% were staged pT2 [4,5,7,16–18]. An increase in organ-confined tumours over time, as in the present series, was noted by others [4,16].

The 10% overall proportion with seminal vesicle invasion is at the upper end of the 5–11% reported by other large series [1,4,5,7,18,23]. Conversely, the 2% incidence of pelvic lymph node metastases is at the lower end of the range reported in the same publications (2–8%).

Tumour at an inked circumferential limit is a significant predictor of disease progression [1,2,4,5,11,14,18,29,36–39], supported by multivariate analysis [1,5,14,38,40,41], and with few dissenters [3]. The prognostic significance of a tumour-positive intraprostatic margin has also been established [4,14,38,39,42,43], although its significance in predicting early recurrence is not supported [44]. Important limited positive subgroups are further defined by adding the Gleason score [1,16,23,42], extent of extraprostatic spread [14,36] and positive margin site [14,42], although precise definitions are not agreed.

Positive circumferential margins were found in 291/968 (29%) cases and as the solitary positive margin in 107 (10.7%). In 122 (12.2%) of patients, limit positivity was associated with extraprostatic tumour. In comparison with other series from 1977 to 1999, positive circumferential limits were reported in 34%, 20% and 10.2%, respectively [2,16,38]. In the present series, 58% of the positive circumferential limits were intraprostatic, within the 24–66% reported [4,38,39,42].

There was a significant decline over time for extraprostatic limit-positive disease, as previously recorded [17,34], but this change was not detected for intraprostatic limit-positive disease.

In the current series tumour was present in the bladder neck margin in 67 (7%) of 968 of patients, compared with 3.6–8.7% reported previously [14,37,45,46]. In the present series a bladder neck margin was the solitary positive margin in only 10 (1%) of 968 cases. This incidence is similar to that in other series [29], in which it was also noted that bladder neck involvement is associated with other adverse prognostic factors [47].

The presence of carcinoma in apical limits is a significant predictor of relapse [2,4,14,37], albeit only on univariate analysis [2,37]. In the present series apical margins were positive in 370/968 (37%) of specimens, constituting 74% [370/502] of all positive margins and 64% [215/336] of single-site positive margins. These values compare with those published previously of positive apical margins of 12–41% [2,29,37–39]. The present findings support the prime importance of the apex as a margin-positive site, but our values are higher than in other series, some of which excluded men with extraprostatic disease, seminal vesicle or lymph node involvement [37,38].
The overall limit positive rate of 52% is similar to the 46% reported in the 1986-99 consecutive series from Australia [4] and the 41% in the 1982-88 series from Johns Hopkins, which excluded higher-stage disease, constituting 15% of their consecutive series [14]. Most publications give an overall limit-positive rate of 23-39% [1,11,29,36,38,39]. In the recent results from Johns Hopkins, in which only 3.7% were excluded from 2370 consecutive patients operated on between 1982 and 1998, only 11% had carcinoma at any resection margin [16].

Attention has been drawn to the relationship between risk of relapse and the number of positive margins, a solitary margin occurring in 27% and 21%, more than one in 18% and 7% of all cases, respectively [4,6]. In the present series the comparable values were 35% with single limit-positive disease and 18% with multiple limit-positive disease.

In conclusion, the results of this UK RP series mirrors that of other unscreened populations reported from Europe, the USA and Australia. Since the advent of PSA testing in the UK, this and other series show a stage migration; more men are currently found to have organ-confined, margin-negative prostate cancer at RP. The results of large European and North American screening trials are awaited to see whether PSA screening will have a further effect on pathological outcome and, more importantly, overall survival in men with prostate cancer.

ACKNOWLEDGEMENTS

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CONFLICT OF INTEREST

None declared.

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Correspondence: Simon Bott, Department of Urology, Royal Surrey County Hospital, Edgerton Road, Guildford, Surrey, GU2 5XX, UK. e-mail: simonrbott@hotmail.com

Abbreviations: RP, radical prostatectomy; UCL/UCUH, University College London Hospitals; NHS, National Health Service.
Initial incision of lateral pelvic fascia and early ligation of vascular pedicles during radical prostatectomy: potential to reduce positive margin rates

MARC RICHMAN, SEAN MCLAUGHLIN, SUSAN MAYGARDEN and RAJ S. PRUTHI
Division of Urologic Surgery, The University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA
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OBJECTIVE
To report on our experience with a recently published technique to reduce positive margin (PM) rates (involving early incision of the lateral pelvic fascia, early release of the prostate and Denovilliers’ fascia off the rectum), with the additional modification of early ligation of the lateral vascular pedicles during radical retropubic prostatectomy (RP), as reducing PM rates continues to be an important oncological goal in RP.

PATIENTS AND METHODS
One hundred consecutive men (mean age 61 years, pretreatment prostate-specific antigen level 8.9 ng/mL, and estimated blood loss 502 mL) underwent RP by one surgeon. The initial dissection involves early incision of the lateral pelvic fascia and developing the plane between the prostate and underlying rectum, before any apical dissection. This incision can be made medial to the neurovascular bundles in a nerve-sparing procedure. After this plane is developed, the lateral vascular pedicles to the prostate are also divided. Once these same manoeuvres are used contralaterally, the prostate is lifted off the apex and bladder neck. The apical (urethral) dissection is then carried out conventionally, followed by dissection/puncture of the seminal vesicles and the bladder neck.

RESULTS
The pathological stage included T2a (11%), T2b (69%), T3a (17%), T3b (3%), and N+ (2%); 20 patients had capsular penetration, at the posterolateral (in 15) and anterior aspect (in five) of the gland. The PM rate for the 100 consecutive patients was 13%, with PMs at the apex in 10, the base in two and posterolateral gland in one. No patient had a PM at the site of capsular penetration. When patients were stratified by low-moderate risk (pT2 and Gleason sum ≤7) vs high risk (pT3 or Gleason sum >7), the PM rates were 7.9% and 29.2%, respectively.

CONCLUSIONS
Initial dissection of the lateral pelvic fascia, including developing a ‘periurethral pocket’, and early ligation of the lateral pedicles, resulted in a low PM rate during RP. This experience supports the previous observations that early development of the pre-rectal fat plane may allow for more precise dissection below all layers of Denovilliers’ fascia and with a wider margin of periprostatic tissue.

KEYWORDS
prostatectomy, radical, cancer, prostate, recurrence

INTRODUCTION
Contemporary radical prostatectomy (RP) has had a major effect on the treatment, outcome and possibly even survival of patients with localized prostate cancer [1]. Refinements in surgical technique have helped to minimize both the short- and long-term morbidity of this procedure. Such technical improvements have also been important in improving oncological outcomes. Contemporary series have shown improved biochemical disease-free survival rates in men undergoing RP [2–6]. Undoubtedly, modern series reflect the stage migration associated with more favourable, PSA-detected tumours [3,4,6]. However, the role of surgical refinement may also be important in improving disease-specific recurrence and survival. A better understanding of the pathological behaviour of prostate cancer, including the protective role of including Denovilliers’ fascia in the surgical specimen, has been one area in which surgical technique may have contributed to disease outcome [7,8]. Perhaps most significant has been the improved understanding of the prognostic impact of positive surgical margin (PM) status on disease recurrence [9–13]. Certainly, surgical technique can affect margin status, and refinements to reduce PMs may thus be important in improving the oncological outcome.

Recently, Stephenson et al. [14] and Klein et al. [6] reported a reduction in PM rate associated with a modification of the surgical extirpative procedure. This technique involves the early incision of the lateral pelvic fascia and subsequent early release of the prostate and Denovilliers’ fascia off the rectum. A detailed evaluation of the effect of this technique suggested, on logistic regression analysis, that early development of the plane between the prostate and rectum (pre-rectal fat plane) may itself result in halving the PM rates [6]. We report on our experience with this technique of a priori incision of the lateral pelvic fascia and early dissection of the pre-rectal fat plane, with the additional modification of early ligation of the lateral vascular pedicles to the prostate during RP.

PATIENTS AND METHODS
One hundred consecutive men had a retropubic RP by one urological surgeon (R.S.P.) between January 2002 and March
2003; all had a standard RP, as described below, for clinically localized disease (clinical stage T1, T2). No patient had received any preoperative neoadjuvant therapy; their characteristics are shown in Table 1. The outcome (continence and potency) was assessed at 1 year by a telephone interview conducted by an independent surveyor. Continence is reported as the number of pads used per day, and potency defined as ‘erections sufficient for intercourse to your and your partner’s satisfaction’. The 1-year potency rates described here include erections obtained with or without the use of a phosphodiesterase-5 inhibitor.

All prostate specimens were analysed routinely and according to the sampling method described by Hall et al. [15]; briefly, the prostate was fixed for 24 h in formalin, the specimen orientated, and the right and left sides inked in different colours. The apex and base margin slices were then removed from the specimen, cut radially and submitted in their entirety. The seminal vesicles and vas deferens were sampled at their junction with the prostate. The slice next to the apical margin was assessed totally and then alternating serial slices of the posterior half of the remainder of the gland evaluated.

SURGICAL TECHNIQUE

A limited infra-umbilical incision (~10 cm) is used to gain access to the space of Retzius, and a Bookwalter retractor used throughout for adequate retraction and exposure. A malleable retractor is placed to pull the bladder to one side, to expose the obturator node packet and the endopelvic fascia. The endopelvic fascia is opened with electrocautery and a right-angle clamp, and the lateral pelvic (peri-prostatic) fascia exposed (Fig. 1). Below this fascial layer, the neurovascular bundle (NVB) is easily visualized as it tails laterally away from the prostate at the level of the prostatic base. In a nerve-sparing procedure, the lateral pelvic fascia is incised sharply between the NVB and prostate (Fig. 1). This plane is developed from the base to beyond the apex, allowing the NVB to fall laterally away from the prostate gland.

The plane between the prostate and encompassing Denovilliers’ fascia and underlying rectum is then developed [‘perirectal pocket’], often with the assistance of a right-angle clamp and the surgeon’s index finger (Fig. 2a,b). Care should be taken to remain below the layers on Denovilliers’ fascia (i.e. in the pre-rectal fat plane) to avoid inadvertent capsular incision and a PM. Blunt development of this plane with the surgeon’s index finger may help to avoid iatrogenic capsular incision. After this plane is developed, the lateral vascular pedicles to the prostate are isolated, secured with a right-angle clamp, divided and ligated (Fig. 3). Once these same manoeuvres are used contralaterally, the prostate is lifted off the rectum and held in place only by the apex and bladder neck.

For the apical dissection, a back-bleeding suture is placed, followed by ligation of the dorsal venous complex (Fig. 4). The complex is divided, exposing the anterior urethra, which is partly transected, leaving the posterior urethra intact. This helps to prevent retraction of the urethra while placing the anastomotic sutures, which is done at this point. Next, the posterior urethra and rectourethralis are transected and the prostatic apex lifted free, as the posterior dissection is completed. After
inserting the urethral catheter into the prostatic apex for retraction, the ipsilateral vas deferens and seminal vesicle are dissected together, and clamped and ligated together beyond the tip of the seminal vesicle. The bladder neck is then dissected and transected. We often spare the bladder neck if there is no evidence of tumour extension at the prostatic base. The pre-positioned urethral anastomotic sutures are then placed in the appropriate positions in the bladder neck, a new urethral catheter placed, the bladder allowed to descend into the pelvis, and the anastomotic sutures tied.

RESULTS

Table 1 shows the estimated blood loss and pathological outcomes; 20 patients had pathological evidence of capsular penetration (CP), at the posterolateral aspect (in 15) and anterior aspect (in five) of the gland. The rate of PMs for the 100 consecutive patients was 13%; the sites of the PMs are also shown in Table 1. Most PMs were at the apex (10), with only one patient with a PM at the posterolateral aspect of the prostate. No patient had a positive margin located at the site of CP.

Table 1 also shows the PM rates stratified by pathological stage and Gleason grade of the operative specimen; when stratified by pathological stage and grade as low-, moderate- and high-risk the PM rates differed. Although PM rates were higher in African-Americans (18.8% (6/32)) than Caucasian-Americans (10.3% (7/68)), this was not statistically significant.

Continence rates 1 year after RP showed that 94 patients required no pads, four needed one pad/day and two required two pads/day. Of the 57 men who were potent before RP and who had a bilateral nerve-sparing procedure, half were potent (as defined) at 1 year after surgery.

DISCUSSION

Reducing PMs during RP continues to be an important goal, as PMs portend a worse oncological outcome [9–13]. A more careful, anatomical apical dissection with decreased blood loss has been one method by which surgeons have been able to reduce the risk of leaving residual tumour at the margins.

FIG. 2. Creating the ‘peri-rectal pocket’; the plane between the prostate and encompassing Denonvilliers’ fascia and underlying rectum is developed from the base to beyond the apex, allowing the NVB to fall laterally away from the prostate. This plane is developed with Metzenbaum scissors, a right-angle clamp (A), and often with the assistance of the surgeon’s index finger (B).
REDUCING POSITIVE MARGINS AT PROSTATECTOMY

In addition, the importance of an extrafascial dissection (i.e. below all layers of Denonvilliers’ fascia) in reducing PM rates further stresses the importance of surgical dissection on margin status and biochemical outcome [8].

In a series of 53 patients, Stephenson et al. [14] showed that by early incision of the lateral pelvic fascia and creating a ‘peri-rectal pocket’ (i.e. developing the plane between the prostate and rectum) they were able to better create a wide posterior/lateral margin [6]. The PM rate in that initial report on patients not having a nerve-sparing RP was 13%.

Klein et al. [6] further modified the method by applying it to both nerve-sparing and non-nerve-sparing procedures. In the former, the lateral pelvic fascia was incised medial to the NVB, as described above. This series also had lower PM rates (15%) than the 37% rate in patients undergoing the ‘classical’ approach. In the more favourable patient in their series (i.e. clinical stage T1/T2, PSA <10 ng/mL, Gleason sum 6) the PM rates were further reduced to 9%. Even on logistic regression analysis to exclude the possible effect of stage migration and other adverse pathological factors on PM rates, Klein et al. still reported a halving in PM rates, attributable to the modified surgical technique alone.

Our experience likewise shows a low PM rate when using the ‘Stephenson-Klein’ technique of early incision of the lateral pelvic fascia and early dissection of the prostate from the rectum. Similar to the previous reports, the present PM rates were lower (13%) than in other contemporary series using the classical approach, and similarly there was a further reduction in PM rate to 8% in the low and moderate risk cohort (pathological stage T2, Gleason sum 6 or 7), and as low as 2.5% in the low-risk group alone. Our experience supports the results of Stephenson et al., that early development of the post-operative fat plane might allow a more precise dissection below all of the layers of Denonvilliers’ fascia, and with a wider margin of periprostatic tissue. Correspondingly, most of the present PMs were at the apex, with only one patient with a PM at the posterior/lateral margin. Furthermore, of the 20 patients with extracapsular extension, none had a PM at those sites. Nevertheless, care is needed at the posterior dissection between the rectum and prostate, to avoid inadvertent

FIG. 3. Early ligation of lateral vascular pedicles; after the pre-rectal plane is developed, the lateral vascular pedicles to the prostate are isolated, secured with a right-angle clamp, divided and ligated. The lateral pedicles are divided close to the prostate to avoid injury to the NVB, which is easily visualized laterally.

FIG. 4. Apical dissection; after placing a back-bleeding suture, the dorsal venous (DV) complex is ligated distally and then divided using electrocautery, after which the anterior urethra is exposed and partly transected sharply with the Metzenbaum scissors, leaving the posterior urethra intact. This helps to prevent the urethra retracting while placing the anastomotic sutures. The posterior urethra and rectourethralis are then transected and the prostatic apex lifted free.

[16,17].
capsular incision and a resultant PM. Blunt development of this plane using the surgeon’s fingers may help to avoid sharp violation of Denonvilliers’ fascia encompassing the prostate gland at this juncture.

Our experience also supports that of Klein et al. [6] and Ruckle and Zincke [18], that early lateral and posterior dissection facilitates the apical and urethral dissection, especially posteriorly, and thereby helps to reduce the rate of PMs at the prostatic apex. Early dissection below all the layers of Denonvilliers’ fascia allows for a more complete and accurate transsection at the apex, thereby minimizing any residual apical tissue and more convincingly attaining the proper posterior plane below Denonvilliers’ fascia. Furthermore, our modification of early ligation and transection of the lateral prostatic vascular pedicles seems to allow for even better mobilization of the prostate, especially for a more precise dissection of the prostatic apex and posterior urethra. In addition to these advantages, early ligation and transection of the lateral pedicle seems to reduce the blood loss associated with this procedure.

The immediate benefits of a reduction in PM rates and surgical blood loss with this technical modification seemed to be associated with no adverse effects on continence, potency or any other surgical morbidity. Indeed, Ruckle and Zincke, and Klein et al. suggested that this technique may improve the overall ease of RP. Several series have correspondingly reported no compromise of continence with this modification, and our preliminary results seem to confirm this, with 94% of patients having good continence (i.e. no pad use) a year after RP. For potency this initial series is certainly too premature to be analysed for this more long-term outcome, but the 1-year follow-up suggested no compromise in expected potency rates with this technique. Others have suggested that this technique may allow for better visualization of the NVB and a correspondingly better functional outcome [6]. Certainly, the plane between the NVB and the prostate is better defined towards the base of the gland, where the bundles begin to lateralize and course posteriorly (compared with their more intimate proximity at the prostatic apex). Consequently, this may thereby provide the ideal site to start dissecting the NVB off the prostate. No other complications associated with this procedure have been reported in other series. Furthermore, our additional modification of early ligation and transection of the lateral vascular pedicles would not be expected to provide any further added morbidity to this technique. Indeed, there were no added operative risks in our series. Although one patient had a rectal injury it was not thought to be associated with the modified method. The extensive experience of Klein et al. [6] similarly shows no greater risk of rectal injury or other operative complications.

There are several limitations to the present study. First, there were only 100 consecutive patients, but the previous reports [6,14] provide a sound basis for our initial series, and the additional modification does not appear to detract from these results. Nevertheless, a larger cohort would help to validate the initial findings reported here. Second, the present follow-up is limited and provides no assessment of long-term potency or biochemical disease-free survival. Although we would expect reduced PMs to confer better chemical disease-free survival (as shown in many large prostatectomy series and validated prognostic nomograms) the routine long-term follow-up used at our institution will be required [9–13].

In conclusion, low PM rates are associated with the modified technique of RP, as initially described by others [6,14]. The present additional modification of early ligation and dividing the lateral vascular pedicles of the prostate further helps to develop the prostatic apex plane, mobilize the prostate and thereby facilitate apical dissection and devascularization of the prostate. Although initial functional and oncological outcomes in the present series (and in others) appears promising, long-term outcomes will help to validate the potential benefits of this surgical technique.

CONFLICT OF INTEREST

None declared.

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Correspondence: Raj S. Pruthi, Division of Urologic Surgery, The University of North Carolina at Chapel Hill, 2140 Bioinformatics Bldg, CB7235, Chapel Hill, North Carolina 27599, USA.

e-mail: rpruthi@med.unc.edu

Abbreviations: RP, radical prostatectomy; PM, positive margin; NVB, neurovascular bundle; CP, capsular penetration.
INTRODUCTION

Support groups for men with prostate cancer are a method for providing psychological support that appears to be desirable to this patient population [1,2]. Qualitative research suggests that prostate cancer support groups help men by providing information and emotional support, and reducing feelings of isolation [3]. In one large-scale survey, men who attended prostate cancer support groups reported that these groups provided good emotional support [1]. However, previous research has not investigated the extent to which different aspects of support, both positive and negative, are experienced by men attending these groups, or the group and individual variables that are predictive of reporting greater support.

Other research has sought to identify what cohort of men find such groups useful, and who might benefit from this method of support. Katz et al. [4] found that in the USA, men who used these groups had higher levels of education and income, and better quality of life (QoL) than non-participants. By contrast, Balderson and Towell [5] found higher levels of psychological distress in participants of prostate cancer support groups in the UK by comparison to previous studies of general patient groups with prostate cancer [6–8]. Thus, while some urologists are concerned that support-group participants tend to be dissatisfied and unhappy patients, evidence for this is inconsistent and further research is needed [9]. The present study had two main aims. First, we investigated men's reports of the support they received from these groups and identified predictors of support receipt, by developing a new measure, the Prostate Cancer Peer Support Inventory (PCSI). Second, we assessed the socio-demographic, medical and adjustment characteristics of men who attend these groups in Australia.

OBJECTIVE

To develop and test a measure for assessing peer support for men attending prostate cancer support groups, and to describe socio-demographic, medical and adjustment characteristics of Australian men who attend these support groups.

PATIENTS AND METHODS

In all, 1224 men (51% response) from 44 prostate-cancer support groups across Australia were recruited by mail. Men completed self-report measures that included the Prostate Cancer Peer Support Inventory (PCSI), the UCLA Prostate Cancer Index bother scales, psychological distress, quality of life (QoL), bother from pain and tiredness, perception of the clinician's support for group participation. Group-level variables were also included in the analyses.

RESULTS

Peer support was rated positively by most men; a high satisfaction with support groups was related to better QoL, lower pain, younger age, higher perceived clinician support for group participation, use of alternative therapies, lower education, and regular attendance; dissatisfaction with support groups was related to higher psychological distress, lower QoL, and lower perceived clinician support for group participation. Group variables did not predict positive or negative support. Overall QoL was similar to community norms and psychological distress was low, with only 8% of men reporting high distress. The most common physical symptom was sexual bother, with 74% of men reporting moderate or high bother.

CONCLUSIONS

The PCSI was a useful measure of peer support. Perception of the benefits of peer support was related to individual but not group differences. The clinicians' attitudes to participation in support groups influenced the men's experience of these groups, and this finding has implications for developing support services for these men.

KEYWORDS

prostatic neoplasms, peer support, psychological adjustment, support groups
A novel measure, the PCSI, was devised for the current study. A list of 18 possible ways that prostate cancer groups might help men was provided across the domains of informational and decisional support, emotional and practical support, and decreasing social isolation. This list was generated from a review of research in this area and from interviews with men who were members of these groups [11]. Four items were negatively worded. The psychometric properties of the PCSI were examined before the main analyses. A principle-components analysis identified a two-factor solution, accounting for 43.4% of the variance: positive peer support (PPS, 33.2%; \( \alpha = 0.88 \)) and negative peer support (NPS, 10.3%; \( \alpha = 0.55 \)). Composite subscale scores were calculated by summing the items loading on each factor. The correlation between the PPS and NPS was negligible (\( r = -0.06, P = 0.142 \)), showing that the two subscales represented independent facets of the peer-support experience for men in the study.

Also, a series of forced-response questions using tick boxes and Likert-type scales assessed the men’s level of use of support-group services, overall satisfaction with the support provided, and the man’s perception of the extent to which his clinician supported the man’s participation in the support group. Open-ended questions provided men with the opportunity to comment generally on their experiences of the groups.

Psychological distress was measured with the Post-Traumatic Stress Disorder (PTSD) scale checklist (Civilian Version) that assesses symptoms of post-traumatic psychological distress [12]; this scale was previously used on patients with cancer [13]. In the present study, the reliability for the scale was excellent (\( \alpha = 0.93 \)). Total scores of 50 or above on the PTSD indicate consideration for post-traumatic stress disorder. Overall QoL was measured with the generic five-item Satisfaction with Life measure [14], with higher scores indicating a better QoL. In the present study, internal consistency for this measure was good (\( \alpha = 0.89 \)). Domain-specific QoL was assessed using the overall bother subscales of the UCLA Prostate Cancer Index [15]. Items using similar response indicators were included to assess men’s level of bother with pain and tiredness.

STATISTICS

For descriptive data the mean (\( \text{so} \)) is reported and percentages used for individuals who scored above specific thresholds. To examine the impact of support group and individual differences, and variables on the PPS and NPS, a set of mixed-models analyses was used, which are similar to ordinary general linear model analyses except that provision is made for the clustering of individuals’ data within support groups. Unlike previous approaches in which the clustering variable was used to calculate a design effect that in turn was used to adjust the standard errors of analyses, the mixed-models approach builds the clustering variable into the statistical model so that variance associated with it can be estimated more accurately. Before formal analyses, missing values were estimated using a full information maximum likelihood procedure (through SPSS Missing Values Analysis, with the Expectation–Maximization algorithm).

This procedure estimates values missing in a dataset on the basis of values on all existing variables across cases. Simulation studies have shown that maximum likelihood approaches such as Expectation–Maximization are better than all other forms of missing data imputation, including mean substitution and list-wise approaches, in allowing unbiased estimates of population parameters [16]. Following the recommendations of Schafer and Graham [16] only cases with up to half of missing values were retained for the missing-values analysis. In this run, the value of Little’s MCAR test was not significant, indicating that the data were missing completely at random. Data were analysed using SPSS Version 11.5 (SPSS Inc., Chicago, Illinois, USA).

RESULTS

In all, 1224 men (51%) responded; Table 1 describes the demographic and medical characteristics of the participants. Most participants were English-speaking, with 7% reporting that they spoke a language other than English at home. Most men (69%) indicated that their prostate cancer was confined to the prostate; 23% had prostate cancer that had spread outside the prostate and the remaining 8% did not know about the extent of their cancer. Of all the men, 59% reported using alternative therapies. Generally men reported a good overall QoL (mean 23.8, \( SD 7.0 \)). Levels of PTSD symptoms in the group were low (mean 29.1, \( SD 12.36 \)) with only 8% of men scoring above the threshold that would indicate levels of distress consistent with PTSD. Men whose cancer was confined to their prostate had higher satisfaction with life (\( P = 0.002 \)) and lower psychological distress (\( P < 0.001 \)) than men whose cancer was not confined. A minority of men reported moderate to substantial problems with bowel (19%) and urinary function (22%). By contrast, 74% of men reported moderate to substantial problems with initiating and maintaining an erection. Pain was infrequently reported as a moderate or substantial problem (10% of men), and tiredness was reported by 36% of men.

INVOLVEMENT IN SUPPORT GROUP ACTIVITIES

Men had been members of support groups for a mean (\( \text{so} \)) of 29.8 (24.3) months. Most men (80%) had advised their clinician that they

---

### TABLE 1 Demographic characteristics of participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Educational level</td>
<td></td>
</tr>
<tr>
<td>Primary school</td>
<td>11</td>
</tr>
<tr>
<td>Year 10</td>
<td>25</td>
</tr>
<tr>
<td>Year 12</td>
<td>16</td>
</tr>
<tr>
<td>Vocational training</td>
<td>22</td>
</tr>
<tr>
<td>University</td>
<td>25</td>
</tr>
<tr>
<td>Medical treatment*</td>
<td></td>
</tr>
<tr>
<td>Radical prostatectomy</td>
<td>40</td>
</tr>
<tr>
<td>Radiation therapy</td>
<td>41</td>
</tr>
<tr>
<td>Watchful waiting</td>
<td>16</td>
</tr>
<tr>
<td>Not yet had treatment</td>
<td>10</td>
</tr>
<tr>
<td>Hormone therapy</td>
<td>38</td>
</tr>
<tr>
<td>Orchidectomy</td>
<td>5</td>
</tr>
<tr>
<td>Time since diagnosis</td>
<td></td>
</tr>
<tr>
<td>&lt;12 months</td>
<td>17</td>
</tr>
<tr>
<td>1–3 years</td>
<td>32</td>
</tr>
<tr>
<td>&gt;3 years</td>
<td>51</td>
</tr>
<tr>
<td>Married/de facto</td>
<td>84</td>
</tr>
<tr>
<td>Mean (( \text{so} )) age, years</td>
<td>67.6 (7.8)</td>
</tr>
</tbody>
</table>

*For medical treatments received, percentages add up to >100 as some men had received several treatments.
Men were very satisfied with the support they received from support groups; the nature of the support included information, emotional support, and reduced feelings of social isolation. Negative outcomes from participation, e.g. becoming confused about treatments or being uncertain about the future, were uncommon. Consistent with these positive experiences, men in these groups were strong advocates for the use of support groups. The man's report of his clinician's level of support for the man's participation in the group emerged as a predictor of both PPS and NPS, and the support of the clinician was associated with better outcomes. This is the first study to show that the clinician’s response to the man’s involvement in supportive-care activities influences the man’s experience of that activity. As men are reluctant users of psychological support services generally, this is important. Specifically, educational and support-group programmes can improve adjustment after a diagnosis of prostate cancer in a range of indices, such as sexual bother and physical functioning, particularly for men with lower levels of education [17]. However, men look first to their clinicians for support and information about their cancer [18,19], and clinicians’ responses to men’s needs are important for their use of available support services. In addition, our results suggest that clinicians’ attitudes to these services also frame men’s experience of them.

Younger men with lower levels of education reported a greater PPS than older and better-educated men. Previous research has shown that younger men report a greater need for support about sexuality, and that less-educated men have a greater need for help in patient care and support [20]. It might be that these groups are orientated somewhat to these concerns. Use of alternative therapies in this group was higher than reported in previous studies, and was related to satisfaction with support, suggesting that men join these groups partly for advice about such therapies [21–24]. Groups were less helpful for men who were experiencing bother from pain, and the reasons for this are unclear. This might relate to physical limitations from painful symptoms, e.g. group meetings might be more difficult for these men to access. Finally, reporting more unhelpful peer support was related to poorer QoL and higher psychological distress, suggesting that highly distressed men might need additional support. Peer support programmes need to be integrated.

**TABLE 2 Mean scores for the PCSI items**

<table>
<thead>
<tr>
<th>Item</th>
<th>Mean (SD) score</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPS</td>
<td></td>
</tr>
<tr>
<td>Received helpful information and advice about prostate cancer</td>
<td>4.44 (0.94)</td>
</tr>
<tr>
<td>Felt that I understood about prostate cancer better</td>
<td>4.39 (0.98)</td>
</tr>
<tr>
<td>Received helpful information and advice about prostate cancer treatments</td>
<td>4.27 (1.12)</td>
</tr>
<tr>
<td>Knew that someone was always available when I needed help</td>
<td>4.22 (1.18)</td>
</tr>
<tr>
<td>Felt less alone as a man with prostate cancer</td>
<td>3.93 (1.38)</td>
</tr>
<tr>
<td>Felt reassured about my medical treatment</td>
<td>3.91 (1.25)</td>
</tr>
<tr>
<td>I felt more in control of my life</td>
<td>3.87 (1.22)</td>
</tr>
<tr>
<td>Was able to talk about my concerns</td>
<td>3.82 (1.33)</td>
</tr>
<tr>
<td>Realized that having prostate cancer was not my fault</td>
<td>3.78 (1.64)</td>
</tr>
<tr>
<td>Was able to discuss worrying thoughts and emotions</td>
<td>3.66 (1.38)</td>
</tr>
<tr>
<td>Felt reassured about my manhood</td>
<td>3.36 (1.53)</td>
</tr>
<tr>
<td>Received practical advice about coping with incontinence</td>
<td>3.26 (1.60)</td>
</tr>
<tr>
<td>Received practical advice about coping with impotence</td>
<td>2.96 (1.56)</td>
</tr>
<tr>
<td>Received practical advice about coping with bowel problems</td>
<td>2.42 (1.60)</td>
</tr>
<tr>
<td>NPS</td>
<td></td>
</tr>
<tr>
<td>Felt more uncertain about my future</td>
<td>2.12 (1.32)</td>
</tr>
<tr>
<td>Could not find anyone to talk to who was similar to me</td>
<td>1.98 (1.39)</td>
</tr>
<tr>
<td>Became more confused about my treatment choice</td>
<td>1.93 (1.23)</td>
</tr>
<tr>
<td>Could not get in touch with someone when I needed them</td>
<td>1.81 (1.42)</td>
</tr>
</tbody>
</table>

Scores ranged from 1, 'did not happen', to 3, 'happened some of the time' to 5, 'happened most of the time'; for all items raw unadjusted scores are presented.
into a broader service framework to facilitate access across a range of levels of intervention [11].

Overall, men in the present study were well adjusted psychologically, with an overall QoL similar to community norms [14]. The most evident physical adjustment difficulty was sexual dysfunction, followed by tiredness. Our findings do not support the view that these men represent a more highly distressed patient group, as has been suggested by previous studies of men with prostate cancer [6–8].

A limitation of the present study is the cross-sectional design, which means that causality cannot be inferred. In this regard, peer support programmes tend to be community-based and so are not amenable to randomized control designs. Moreover, while our response rate was acceptable for a mail survey of this nature, it might be that men who did not respond differed in some way from those who did. As the survey was anonymous, non-responders could not be followed up. It is possible that non-responders were more dissatisfied with the group support, or were more distressed than responders. Alternatively, non-responders might have been less engaged in the groups. Prospective research to record men’s experiences in these groups over time, assessing aspects such as levels of engagement and how this relates to the process of adjustment, are needed. Finally, we did not survey partners or family members who participate in these groups. The extent to which prostate cancer support groups provide support for the families of men with prostate cancer is a further research question. However, given the continued growth of such groups, studies such as the present, that include a large sample and use a multilevel approach, provide important insights. Also, the development of a measure with good psychometric properties for assessing the helpfulness of support groups, the PCSI, has the potential to advance research in this area.

Peer-support groups provide information and emotional support at a low cost, and decrease social isolation for men with prostate cancer. Factors that predicted high PPS and low NPS were individual variables, and group influences were not significant. Individual factors that are important include age, educational level and pain. A new finding was

### TABLE 3 Predictors of PPS and NPS

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parameter estimate (95% CI)</th>
<th>P</th>
<th>NPS</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attendance</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infrequent</td>
<td>−6.4 (−7.6, −5.1)</td>
<td>&lt;0.01</td>
<td>0.01</td>
<td>−0.3</td>
</tr>
<tr>
<td>Frequent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Educational level</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>primary/junior</td>
<td>2.6 (1.0, 4.2)</td>
<td>&lt;0.01</td>
<td>0.3</td>
<td>−0.2</td>
</tr>
<tr>
<td>senior/TAFE*</td>
<td>2.0 (0.5, 3.6)</td>
<td>0.01</td>
<td>0.2</td>
<td>−0.3</td>
</tr>
<tr>
<td>university</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>How long ago told of cancer, years</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&lt;1</td>
<td>1.5 (−0.7, 3.6)</td>
<td>0.18</td>
<td>−0.2</td>
<td>−0.8</td>
</tr>
<tr>
<td>1–2</td>
<td>0.2 (−1.8, 2.1)</td>
<td>0.88</td>
<td>−0.3</td>
<td>−0.8</td>
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<tr>
<td>2–3</td>
<td>0.1 (−1.7, 1.9)</td>
<td>0.94</td>
<td>−0.2</td>
<td>−0.7</td>
</tr>
<tr>
<td>≥3</td>
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<tr>
<td>Confined tumour</td>
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<td></td>
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<tr>
<td>No</td>
<td>−0.2 (−1.7, 1.3)</td>
<td>0.82</td>
<td>−0.1</td>
<td>−0.6</td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of alternative therapies</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>No</td>
<td>−1.7 (−2.9, −0.4)</td>
<td>0.01</td>
<td>−0.2</td>
<td>−0.5</td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perceived support from clinician</td>
<td>2.6 (2.1, 3.1)</td>
<td>&lt;0.01</td>
<td>−0.2</td>
<td>−0.3</td>
</tr>
<tr>
<td>Length of attendance</td>
<td>0.02 (−0.01, 0.06)</td>
<td>0.15</td>
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<td>−0.01</td>
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<td>Age</td>
<td>−0.14 (−0.22, −0.05)</td>
<td>&lt;0.01</td>
<td>−0.01</td>
<td>−0.04</td>
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<tr>
<td>Bother – urinary</td>
<td>−0.01 (−0.03, 0.01)</td>
<td>0.23</td>
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<td>Bother – sexual</td>
<td>0.01 (−0.01, 0.03)</td>
<td>0.32</td>
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<td>−0.01</td>
</tr>
<tr>
<td>Bother – bowel</td>
<td>−0.01 (−0.03, 0.02)</td>
<td>0.61</td>
<td>0</td>
<td>−0.01</td>
</tr>
<tr>
<td>Bother – pain</td>
<td>−0.9 (−1.5, −0.2)</td>
<td>0.01</td>
<td>0.09</td>
<td>−0.1</td>
</tr>
<tr>
<td>Bother – tiredness</td>
<td>0.4 (−0.2, 0.96)</td>
<td>0.20</td>
<td>−0.04</td>
<td>−0.2</td>
</tr>
<tr>
<td>Overall QoL</td>
<td>0.2 (0.1, 0.3)</td>
<td>&lt;0.01</td>
<td>−0.05</td>
<td>−0.08</td>
</tr>
<tr>
<td>Psychological distress</td>
<td>−0.01 (−0.08, 0.05)</td>
<td>0.70</td>
<td>0.07</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Parameter estimates for discrete variables not given above are equal to zero minus the sum of the remaining parameters for that variable. *TAFE, technical and further education.
that the clinician’s level of support for the man’s participation in the group appears to frame the man’s response to the group support. Clinicians are integral to the development and implementation of support services for men with prostate cancer.

ACKNOWLEDGEMENTS

We gratefully acknowledge Pfizer for providing a grant to support this project. We also thank Dr Stefano Occhipinti for providing comments in the development of this manuscript.

CONFLICT OF INTEREST

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Correspondence: Suzanne Steginga, Director Community services, Queensland Cancer Fund, PO Box 201, Spring Hill QLD 4004, Australia, e-mail: ssteginga@qlcancer.com.au

Abbreviations: PCSI, Prostate Cancer Peer Support Inventory; QoL, quality of life; PPS, positive peer support; NPS, negative peer support, PTSD, post-traumatic stress disorder.
Prostate cancer: socio-economic, geographical and private-health insurance effects on care and survival

SONJA E. HALL, C. D’ARCY J. HOLMAN, Z. STAN WISNIEWSKI* and JAMES SEMMENST
School of Population Health, and †Centre for Health Services Research, The University of Western Australia, Crawley, and *Hollywood Private Hospital, Nedlands, WA, Australia
Accepted for publication 9 August 2004

OBJECTIVE
To examine the effects of demographic, geographical and socio-economic factors, and the influence of private health insurance, on patterns of prostate cancer care and 3-year survival in Western Australia (WA).

PATIENTS AND METHODS
The WA Record Linkage Project was used to extract all hospital morbidity, cancer and death records of men diagnosed with prostate cancer between 1982 and 2001. The likelihood of having a radical prostatectomy (RP) was estimated using logistic regression, and the likelihood of death 3 years after diagnosis was estimated using Cox regression.

RESULTS
The proportion of men undergoing RP increased six-fold, from 3.1% to 20.1%, over the 20 years, whilst non-radical surgery (transurethral, open or closed prostatectomy) simultaneously halved to 29%. Men who had RP were typically younger, married and with less comorbidity. Patients with a first admission to a rural hospital were much less likely to have RP (odds ratio 0.15; 95% confidence interval, CI, 0.11–0.21), whereas residence alone in a rural area had less effect (0.54, 0.29–1.03). A first admission to a private hospital increased the likelihood of having RP (2.40, 2.11–2.72), as did having private health insurance (1.77, 1.56–2.00); being more socio-economically disadvantaged reduced RP (0.63, 0.47–0.83). The 3-year mortality rate was greater with a first admission to a rural hospital (relative risk 1.22; 95% CI 1.09–1.36) and in more socio-economically disadvantaged groups (1.34, 1.10–1.64), whereas those admitted to a private hospital (0.77, 0.71–0.84) or with private health insurance (0.82, 0.76–0.89) fared better. Men who had RP had better survival than those who had non-radical surgery (4.85, 3.52–6.68) or no surgery (6.42, 4.65–8.84), although this may be an artefact of a screening effect.

CONCLUSION
The 3-year survival was poorer and the use of RP less frequent in men from socio-economically and geographically disadvantaged backgrounds, particularly those admitted to rural or public hospitals, and those with no private health insurance.

KEYWORDS
radical prostatectomy, geographical, socio-economic disadvantage, private health insurance, record linkage

INTRODUCTION
In Western Australia (WA), 1993 was a watershed year for prostate cancer; although available since 1989, PSA testing became separately itemized on the Medicare Benefits Schedule in November 1993 [1]. In that year overseas urologists arrived in Perth, with new surgical techniques and more aggressive approaches to prostate-cancer care. Furthermore, 1993 saw the beginning of Prostate Awareness Week in Perth, which provided free PSA testing [2]. Dramatic increases in the apparent incidence of prostate cancer were taking place across Australia, not because the underlying biological rate was changing, but because PSA testing allowed earlier latent cancers to be detected. In addition, more surgical procedures for supposed benign prostatic lesions were detecting more cancers [1,2]. In contrast, mortality from prostate cancer has remained stable [1,2].

The main approaches to the care of localized prostate cancer are radical prostatectomy (RP), radiotherapy or combinations of these [3]. There have been no adequate randomized control trials to evaluate which of these options gives the best outcome for survival and quality of life [3–7]. For men presenting with metastasized tumours, palliation and the relief of symptoms are the mainstay of therapy, using hormone suppression or TURP to relieve outlet symptoms. These men, especially if younger, should be diagnosed at an earlier stage when curative treatment may be considered, and thus patterns of non-radical surgery in younger men reflect a lack of early evaluation and opportunities for cure.

Curative radiotherapy is a newer treatment, and as an outpatient procedure is not recorded in the population databases used for the present study. As the present study was population-based and covered 20 years of prostate cancer care, it focuses on surgical intervention, particularly RP. The first aim therefore was to describe the patterns of surgical care and survival outcome in men diagnosed with prostatic cancer in WA.

Australia has universal publicly funded healthcare, provided in tandem with private-sector services funded through individual payments, with community risk pooling. The private health-insurance industry is subsidized by tax rebates. Patients with private health cover can choose to access private or public hospitals, and those with no cover have ‘out-of-pocket’ costs if they wish to enter the private system [8]. Commentators
have said that this has led to a two-tier system, for the rich and the poor, with implications for treatment patterns and survival in economically disadvantaged groups [9].

Previous studies have shown that there are socio-economic gradients in who has a PSA test, with the more socio-economically advantaged more likely to be tested earlier, especially in the younger groups [1]. Although rural and remote areas of WA initially lagged behind in the apparent incidence of prostate cancer, by 1996 similar rates were reported as in the metropolitan area [1]. The question remains as to whether men from more socio-economically deprived groups or those from non-metropolitan areas receive the same treatment for their prostate cancer as the less disadvantaged groups. In addition, the influence of the private health system on prostate cancer care has not been documented in Australia. The issues of socio-economic and geographical inequalities in prostate cancer care therefore warrant investigation, and the second aim of this study was to address these important questions on equality of care.

PATIENTS AND METHODS

The WA Record Linkage Project [10] was used to extract all state cancer registrations, death records and hospital morbidity records of all men resident in WA diagnosed with primary prostate cancer in the WA Cancer Registry (International Classification of Diseases, ICD-9-85 and ICD-10-AM C61 [11,12]) from 1 January 1982 to 31 December 2001. The data were extracted on 18 June 2003; this allowed for prostate cancer-related hospital admissions, e.g. for surgery, during 2002 to be captured.

A chain of records was formed for each patient, consisting of rows of hospital admission information to which the cancer and death registry information was appended. The first hospital admission with a mention of a diagnosis of prostate cancer or with a prostate procedure was termed the index admission (11 773). However, in 17% of cases there was no hospital admission with a mention of prostate cancer, and in these cases the first hospital admission after the date of prostate cancer registration was used (2350). In either group, the index record had to be within 1 year before and 10 years after the date of prostate cancer registration. In both groups, almost all index records (90%) were within a year of the prostate cancer registration. The mean (±) time for cases with an index record for prostate cancer was 0.45 (1.34) years, and for the combined group 0.55 (1.47) years. The index record provided demographic data plus hospital and private health insurance status, and whether the hospital was metropolitan or rural. Regression models using only those with a prostate cancer admission (11 773) and both groups (14 123) were constructed. The odds ratios (OR) and relative risk (RR) were stable, and the significance levels remained the same; therefore results from the combined groups are reported here, as in addition this captures patients treated with a ‘watchful waiting’ approach.

The Charlson comorbidity index was used to adjust for the effects of comorbidity in the regression analysis [13–15]. This index consisted of 17 groups of ICD codes weighted according to mortality risk (prostatic neoplasms not included); the total weighted index was divided into three intervals. Only comorbidity identified from hospital morbidity records at the time of the prostate cancer registration or in the previous 365 days before the registration contributed to the index.

The year of prostate cancer diagnosis was categorized into three groups. These were determined from several factors, primarily before, during and after the PSA testing years, assigned based on the work by Threlfall et al. [2]. These categories were substantiated by also being before, during and after the change in surgeons in Perth. The surgical rates were plotted and three distinct surgical patterns detected (Fig. 1).

To examine the effect of socio-economic disadvantage on treatment patterns and survival we assigned to each record an index of relative socio-economic disadvantage (IRSD) as published from WA collection district census data for 1991 and 1996. Based on household and individual attributes, the IRSD had five categories, dividing the population into quartiles of disadvantage, with the lowest quartile further subdivided into the 15% and 10% most disadvantaged [16]. Likewise, the Accessibility/Remoteness Index of Australia (ARIA) was assigned to each collection district [17]. In cases where the IRSD or ARIA remained unavailable, the postcode was used. Analysis using IRSD or ARIA codes was restricted to admissions after 1 January 1991, when collection districts first became available via address mapping.

For the analysis of the patterns of surgical care, prostate cancer treatment was defined as radical surgery, non-radical surgery (e.g. TURP, open or closed prostatectomy or destruction of tissues) or non-surgical intervention. The chi-square analysis was undertaken using the three groups. Crude and adjusted logistic regression analyses of the likelihood of having RP rather than non-radical or no surgery were used to allow a comparison of the RP approach and all other approaches, e.g. conservative ‘watchful waiting’, curative radiotherapy and any other pattern of care. Cox regression models of the all-cause likelihood of death at 3 years after prostate cancer diagnosis were constructed; these were checked to ensure that the proportional-hazards assumption was met. The 3-year survival models are reported, as 1 year was considered too short to assess prostate cancer outcome, and the patients diagnosed in the most recent calendar period had not yet had 5 years of follow-up. In all regression models for the age variable, the Box-Tidwell term (age \times \ln age) was used to produce the best-fit model for adjustment purposes [18]. The Human Research Ethics Committee of the authors’ institution granted the study ethical approval.

RESULTS

RP was the primary surgical treatment in 1787 (12.7%) men, whilst 5770 (40.8%) had
non-radical surgery, leaving 6566 (46.5%) men with no surgical intervention. Of those who had non-radical surgery, 86 (1.5%) had a follow-up RP. A death was recorded for 6873 (48.7%) of the cases, and of these, 2402 (34.9%) had prostate cancer recorded as the underlying cause of death.

The proportion of men having RP increased seven-fold over the study period and was accompanied by a halving in the proportion of men having non-radical surgery (Fig. 1 and Table 1). Men were considerably more likely to have RP in the period after PSA testing was introduced, especially if younger, married and with less comorbidity (Tables 1 and 2). Men who were more socio-economically advantaged or had private health insurance were more likely to have RP, but when the other variables of disadvantage were entered into the model, the effect of private health insurance was lost.

The 3-year cumulative incidence of survival was much better after a diagnosis in 1993–96 and 1997–2001 (Fig. 2). Cox regression models of the all-cause likelihood of death at 3 years (Table 3) showed that men were much less likely to die after a diagnosis of prostate cancer if they were diagnosed in the more recent periods, were younger, had less comorbidity and were described as either being presently married/de facto or divorced/separated, rather than never married or widowed. Men who had a RP were significantly less likely to die than those who did not have a surgical procedure or who had non-radical surgery, although this may have been a result of non-surgical factors. Men who had their first admission to a rural hospital, a public hospital or had no private health insurance, and men from socio-economically disadvantaged groups or living in rural areas, were also much more likely to die; however, men in remote areas did not fare worse. Some of these risk factors were

---

**TABLE 1**


<table>
<thead>
<tr>
<th>Category (N total)</th>
<th>n (%) per category</th>
<th>Radical surgery, %</th>
<th>Non-radical surgery, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calendar year of diagnosis (14 123)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1982–92</td>
<td>4 838 (34.3)</td>
<td>3.1†</td>
<td>59.4‡</td>
</tr>
<tr>
<td>1993–96</td>
<td>4 967 (35.2)</td>
<td>7.3</td>
<td>31.2</td>
</tr>
<tr>
<td>1997–2001</td>
<td>4 318 (30.5)</td>
<td>20.1</td>
<td>29.2</td>
</tr>
<tr>
<td>Age at admission (14 123)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>3 199 (22.7)</td>
<td>38.7†</td>
<td>26.6‡</td>
</tr>
<tr>
<td>&gt;65 years</td>
<td>10 924 (77.3)</td>
<td>5.8</td>
<td>44.3</td>
</tr>
<tr>
<td>Charlson weighted comorbidity index (14 123)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–2</td>
<td>7 665 (54.3)</td>
<td>18.9†</td>
<td>42.4‡</td>
</tr>
<tr>
<td>3–4</td>
<td>3 425 (24.3)</td>
<td>8.7</td>
<td>44.0</td>
</tr>
<tr>
<td>5–11</td>
<td>3 033 (21.5)</td>
<td>4.2</td>
<td>30.6</td>
</tr>
<tr>
<td>Marital status (14 123)</td>
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<td></td>
<td></td>
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<tr>
<td>Never married</td>
<td>821 (5.8)</td>
<td>10.6†</td>
<td>44.5‡</td>
</tr>
<tr>
<td>Married/de facto</td>
<td>10 500 (74.3)</td>
<td>15.5</td>
<td>39.4</td>
</tr>
<tr>
<td>Divorced/separated</td>
<td>663 (4.7)</td>
<td>12.7</td>
<td>36.2</td>
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<tr>
<td>Widowed</td>
<td>1 834 (13.0)</td>
<td>3.2</td>
<td>45.1</td>
</tr>
<tr>
<td>Unknown</td>
<td>305 (2.2)</td>
<td>6.9</td>
<td>56.4</td>
</tr>
<tr>
<td>Indigenous status (14 123)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not indigenous</td>
<td>14 059 (99.5)</td>
<td>13.3†</td>
<td>40.3‡</td>
</tr>
<tr>
<td>Indigenous</td>
<td>64 (0.5)</td>
<td>3.1</td>
<td>34.4</td>
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<tr>
<td>IRSD 1991–2001 (10 364)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Least disadvantaged, 1</td>
<td>2 912 (28.1)</td>
<td>23.6†</td>
<td>27.4</td>
</tr>
<tr>
<td>2</td>
<td>2 126 (20.5)</td>
<td>19.3</td>
<td>32.8</td>
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<tr>
<td>3</td>
<td>2 986 (28.8)</td>
<td>13.4</td>
<td>36.0</td>
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<tr>
<td>4</td>
<td>1 639 (15.8)</td>
<td>12.8</td>
<td>37.7</td>
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<tr>
<td>Most disadvantaged, 5</td>
<td>701 (6.8)</td>
<td>11.7</td>
<td>35.7</td>
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<td>Insurance status (13 865)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Public</td>
<td>6 698 (48.7)</td>
<td>8.2†</td>
<td>42.5‡</td>
</tr>
<tr>
<td>Private</td>
<td>6 170 (50.3)</td>
<td>18.7</td>
<td>38.2</td>
</tr>
<tr>
<td>Hospital type (14 123)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Public</td>
<td>7 685 (54.5)</td>
<td>6.5†</td>
<td>42.6‡</td>
</tr>
<tr>
<td>Private</td>
<td>6 428 (45.5)</td>
<td>21.4</td>
<td>42.3</td>
</tr>
<tr>
<td>ARIA 1991–2001 (10 392)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very accessible</td>
<td>8 872 (85.4)</td>
<td>17.9†</td>
<td>32.9‡</td>
</tr>
<tr>
<td>Accessible</td>
<td>7 413 (72.2)</td>
<td>11.0</td>
<td>35.7</td>
</tr>
<tr>
<td>Moderate accessible</td>
<td>504 (4.8)</td>
<td>15.1</td>
<td>35.3</td>
</tr>
<tr>
<td>Remote</td>
<td>187 (1.8)</td>
<td>15.0</td>
<td>29.4</td>
</tr>
<tr>
<td>Very remote</td>
<td>86 (0.8)</td>
<td>17.4</td>
<td>26.7</td>
</tr>
<tr>
<td>Location of hospital where first admitted (14 123)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metropolitan</td>
<td>12 462 (88.3)</td>
<td>14.7†</td>
<td>41.3‡</td>
</tr>
<tr>
<td>Rural</td>
<td>1 661 (11.7)</td>
<td>2.30</td>
<td>32.6</td>
</tr>
</tbody>
</table>

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modified in the fully adjusted model and these were explored further. In the case of hospital location, each of the other factors of disadvantage individually reduced the RR from 1.22 to 1.00. Moreover, re-running the survival analysis without adjusting for surgical status gave a similar RR of 1.08 (95% CI 0.91–1.28). The RR for insurance status was modified by the hospital location, the IRSD and the ARIA, but not by the hospital status.

DISCUSSION

Prostate cancer is a significant public-health issue in Australia, with continuing debate about testing, treatment and survival [1,4,19,20]. There was a considerable change in treatment patterns over the 20 years of the study, with a shift from non-radical surgery to RP, probably driven by an earlier identification of the cancer, coupled with increasing clinical knowledge and skills over this period. However, the change was not equally distributed among all men, with those in disadvantaged groups continuing to be less likely to have radical surgery.

In WA, the proportion of men diagnosed with prostate cancer treated by RP increased seven-fold, from 3% in the 1980s to 20% in 1997–2000. During the late 1980s and 1993–2000, a third (36%) of men aged ≤65 years had RP, compared to 5% of men aged >65 years. During the late 1980s and before 1993, proportions of 38% [5] to 50% [21] were reported from the USA. The use of population-based data has many advantages [22,23] but the cancer registries in Australia do not routinely compile staging information, therefore prostate cancer staging was unavailable. It is plausible that earlier cancer stage could explain the higher RP fraction in the USA, as testing may have been more common earlier than in Australia [24], albeit that Australian rates continue to be lower than those reported from the USA [5,20]. The lower rate of RP in geographically and socio-economically disadvantaged groups also raises the possibility that a de facto screening process may have operated in metropolitan and higher socio-economic areas, leading to earlier diagnosis and the opportunity for more successful treatment regimens in these groups, and possibly better survival [2]. This may be because screening for prostate cancer is not being supported by published reports and therefore not incorporated into clinical best-practice guidelines [19,20,24,25].

There were substantial improvements in case survival after the introduction of PSA testing in 1993, and the move towards more aggressive surgical intervention. Health Department data from 1982 to 2002 indicated that the age-standardized mortality rate for prostate cancer in WA increased during the 1990s, but has since declined to levels of the 1980s (Fig. 3). These results were congruent with the assessment of Threlfall et al. [2], who found minor increases in the mortality rate in men aged >60 years up to 1996, but no real difference in the long-term trend. This increase to 1994 followed by a decline was reported elsewhere for Australia as a whole [3,20,26], the UK and the USA [27]. In contrast, the all-cause age-standardized mortality rates for WA men declined over this 20-year period.

**TABLE 2 Logistic regression analysis of the likelihood of having RP rather than non-radical or no surgery for primary prostate cancer according to demographic, social and geographical disadvantage, and having private health insurance**

<table>
<thead>
<tr>
<th>Factor</th>
<th>1982–2001 Crude OR (95% CI)</th>
<th>1982–2001 Adj OR (95% CI)^</th>
<th>1991–2001 Adj OR (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calendar period (by year of diagnosis)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1982–92</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>1993–96</td>
<td>6.63 (5.54–7.93)</td>
<td>5.27 (4.35–6.38)</td>
<td>1.99 (1.53–2.58)</td>
</tr>
<tr>
<td>1997–2001</td>
<td>7.95 (6.64–9.52)</td>
<td>6.00 (4.94–7.29)</td>
<td>2.35 (1.81–3.06)</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per year</td>
<td>0.84 (0.84–0.85)</td>
<td>0.85 (0.85–0.86)</td>
<td>0.85 (0.84–0.86)</td>
</tr>
<tr>
<td>Charlson (weighted comorbidty index)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>1–2</td>
<td>0.41 (0.36–0.47)</td>
<td>0.42 (0.35–0.72)</td>
<td>0.63 (0.53–0.74)</td>
</tr>
<tr>
<td>3–15</td>
<td>0.19 (0.16–0.23)</td>
<td>0.35 (0.29–0.44)</td>
<td>0.37 (0.30–0.46)</td>
</tr>
<tr>
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<td>0.11 (0.02–0.75)</td>
<td>0.11 (0.02–0.85)</td>
<td>0.19 (0.02–1.48)</td>
</tr>
<tr>
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<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Married/defacto</td>
<td>1.54 (1.23–1.94)</td>
<td>1.85 (1.42–2.41)</td>
<td>1.57 (1.19–2.09)</td>
</tr>
<tr>
<td>Divorced/separated</td>
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<td>1.01 (0.70–1.46)</td>
<td>0.98 (0.67–1.45)</td>
</tr>
<tr>
<td>Widowed</td>
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<td>1.18 (0.80–1.75)</td>
<td>1.37 (0.90–2.09)</td>
</tr>
<tr>
<td>Unknown</td>
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<td>1.00 (0.57–1.76)</td>
<td>1.39 (0.76–2.53)</td>
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<tr>
<td>IRSD 1991–2001</td>
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<td>Least, 1</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>2</td>
<td>0.78 (0.68–0.89)</td>
<td>0.79 (0.67–0.94)</td>
<td>0.89 (0.75–1.05)</td>
</tr>
<tr>
<td>3</td>
<td>0.50 (0.44–0.57)</td>
<td>0.57 (0.48–0.67)</td>
<td>0.71 (0.59–0.84)</td>
</tr>
<tr>
<td>4</td>
<td>0.47 (0.40–0.56)</td>
<td>0.68 (0.56–0.83)</td>
<td>0.88 (0.72–1.09)</td>
</tr>
<tr>
<td>Most, 5</td>
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<td>0.63 (0.47–0.83)</td>
<td>0.90 (0.66–1.21)</td>
</tr>
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<td>Insurance status</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Private</td>
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<td>1.77 (1.56–2.00)</td>
<td>0.72 (0.58–0.89)</td>
</tr>
<tr>
<td>Hospital status</td>
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<td>2.40 (2.11–2.72)</td>
<td>2.64 (2.11–3.29)</td>
</tr>
<tr>
<td>ARIA 1991–2001</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Very accessible</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Accessible</td>
<td>0.57 (0.45–0.72)</td>
<td>0.63 (0.48–0.83)</td>
<td>1.03 (0.76–1.38)</td>
</tr>
<tr>
<td>Moderate accessible</td>
<td>0.81 (0.62–1.05)</td>
<td>0.74 (0.55–0.98)</td>
<td>1.21 (0.87–1.69)</td>
</tr>
<tr>
<td>Remote</td>
<td>0.81 (0.54–1.21)</td>
<td>0.49 (0.31–0.78)</td>
<td>0.71 (0.43–1.15)</td>
</tr>
<tr>
<td>Very remote</td>
<td>0.97 (0.55–1.70)</td>
<td>0.54 (0.29–1.03)</td>
<td>0.80 (0.40–1.59)</td>
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<tr>
<td>Location of hospital</td>
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<td></td>
<td></td>
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<tr>
<td>Rural</td>
<td>0.14 (0.10–0.19)</td>
<td>0.15 (0.11–0.21)</td>
<td>0.19 (0.13–0.28)</td>
</tr>
</tbody>
</table>

^For the adjusted OR 1982–2000, each factor was adjusted for age, Box-Tidwell transformation of age, calendar period, Charlson index, indigenous status and marital status, except where it was the factor of interest; †For the adjusted OR 1991–2000, each factor was adjusted as for * plus ARIA, IRSD, location and status of hospital, and insurance status, except where it was the factor of interest.
TABLE 3 Cox regression analysis of the likelihood of death from any cause during the 3 years after a diagnosis of prostate cancer, according to demographic, social and geographical disadvantage, and having private health insurance

<table>
<thead>
<tr>
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<tr>
<td>Calendar period (by year of diagnosis)</td>
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<td></td>
</tr>
<tr>
<td>1982–92</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
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<tr>
<td>1993–96</td>
<td>0.30 (0.28–0.32)</td>
<td>0.37 (0.34–0.40)</td>
<td>0.59 (0.51–0.67)</td>
</tr>
<tr>
<td>1997–2001</td>
<td>0.32 (0.29–0.35)</td>
<td>0.35 (0.30–0.39)</td>
<td>0.54 (0.46–0.63)</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per year</td>
<td>1.09 (1.08–1.09)</td>
<td>1.06 (1.05–1.06)</td>
<td>1.07 (1.06–1.07)</td>
</tr>
<tr>
<td>Charlson (weighted comorbidity index)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>1–2</td>
<td>1.76 (1.60–1.94)</td>
<td>1.44 (1.30–1.59)</td>
<td>1.57 (1.37–1.81)</td>
</tr>
<tr>
<td>3–14</td>
<td>4.33 (3.97–4.71)</td>
<td>3.00 (2.74–3.28)</td>
<td>3.56 (3.13–4.05)</td>
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<td>Indigenous status</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Indigenous</td>
<td>1.48 (0.91–2.42)</td>
<td>0.84 (0.51–1.40)</td>
<td>1.00 (0.46–2.15)</td>
</tr>
<tr>
<td>Marital status</td>
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<td></td>
<td></td>
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<tr>
<td>Never married</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Married/de facto</td>
<td>0.66 (0.58–0.76)</td>
<td>0.72 (0.62–0.83)</td>
<td>0.71 (0.58–0.87)</td>
</tr>
<tr>
<td>Divorced/separated</td>
<td>0.71 (0.57–0.87)</td>
<td>0.78 (0.62–0.98)</td>
<td>0.73 (0.54–0.99)</td>
</tr>
<tr>
<td>Widowed</td>
<td>1.56 (1.35–1.80)</td>
<td>0.93 (0.79–1.10)</td>
<td>0.90 (0.71–1.13)</td>
</tr>
<tr>
<td>Unknown</td>
<td>0.88 (0.69–1.14)</td>
<td>0.87 (0.65–1.16)</td>
<td>1.04 (0.74–1.47)</td>
</tr>
<tr>
<td>Surgery</td>
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<td></td>
<td></td>
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<tr>
<td>Radical</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Non-radical</td>
<td>1.65 (1.08–1.92)</td>
<td>1.44 (1.30–1.59)</td>
<td>1.57 (1.37–1.81)</td>
</tr>
<tr>
<td>No surgery</td>
<td>16.94 (12.48–23.00)</td>
<td>6.42 (4.65–8.84)</td>
<td>6.40 (4.41–9.29)</td>
</tr>
<tr>
<td>IRSD 1991–2001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Least,</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>2</td>
<td>1.24 (1.08–1.43)</td>
<td>1.29 (1.11–1.51)</td>
<td>1.24 (1.07–1.45)</td>
</tr>
<tr>
<td>3</td>
<td>1.44 (1.27–1.63)</td>
<td>1.22 (1.06–1.40)</td>
<td>1.14 (0.98–1.32)</td>
</tr>
<tr>
<td>4</td>
<td>1.44 (1.25–1.67)</td>
<td>1.29 (1.10–1.51)</td>
<td>1.23 (1.05–1.45)</td>
</tr>
<tr>
<td>Most, 5</td>
<td>1.83 (1.53–2.20)</td>
<td>1.34 (1.14–1.64)</td>
<td>1.22 (0.99–1.50)</td>
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<td>Insurance status</td>
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<td>0.82 (0.76–0.89)</td>
<td>0.89 (0.77–1.03)</td>
</tr>
<tr>
<td>Hospital status</td>
<td>0.77 (0.71–0.84)</td>
<td>0.88 (0.76–0.99)</td>
<td></td>
</tr>
<tr>
<td>Private</td>
<td>0.39 (0.36–0.42)</td>
<td>0.77 (0.71–0.84)</td>
<td>0.88 (0.76–0.99)</td>
</tr>
<tr>
<td>Very accessible</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Accessible</td>
<td>1.40 (1.19–1.65)</td>
<td>1.18 (0.99–1.41)</td>
<td>1.12 (0.92–1.35)</td>
</tr>
<tr>
<td>Moderate accessible</td>
<td>1.42 (1.17–1.74)</td>
<td>1.40 (1.13–1.74)</td>
<td>1.32 (1.04–1.66)</td>
</tr>
<tr>
<td>Remote</td>
<td>0.99 (0.69–1.42)</td>
<td>1.07 (0.72–1.57)</td>
<td>1.00 (0.68–1.47)</td>
</tr>
<tr>
<td>Very remote</td>
<td>0.56 (0.29–1.08)</td>
<td>0.71 (0.36–1.07)</td>
<td>0.68 (0.34–1.35)</td>
</tr>
<tr>
<td>Location of hospital</td>
<td>1.44 (1.31–1.59)</td>
<td>1.22 (1.09–1.36)</td>
<td>1.00 (0.84–1.18)</td>
</tr>
</tbody>
</table>

*For the adjusted RR 1982–2000, each factor was adjusted for age, Box-Tidwell transformation of age, calendar period, Charlson index, indigenous status, marital status and surgical status, except where it was the factor of interest.; †For the adjusted RR 1991–2000, each factor was adjusted as for *, plus ARIA, IRSD, location and status of hospital, and insurance status, except where it was the factor of interest.

In this study, men admitted to private hospitals had much higher rates of RP and better survival. Typically men with access to private healthcare are more socio-economically advanced, with higher levels of education, which may lead to more demand for screening [19] and active rather than conservative treatment. In addition, radiotherapy facilities are often more comprehensive in public hospitals and therefore there may be less curative radiotherapy used in the private sector; this may explain the pattern of surgical intervention, but not the additional survival seen in private hospital patients, even after adjusting for other factors such as comorbidity.

Australia has a pluralist health system, with a large private hospital sector supported by private health insurance. In this study, men admitted to private hospitals had much higher rates of RP and better survival. Typically men with access to private healthcare are more socio-economically advanced, with higher levels of education, which may lead to more demand for screening [19] and active rather than conservative treatment. In addition, radiotherapy facilities are often more comprehensive in public hospitals and therefore there may be less curative radiotherapy used in the private sector; this may explain the pattern of surgical intervention, but not the additional survival seen in private hospital patients, even after adjusting for other factors such as comorbidity.

In California [5], Virginia [7] and the UK [6] there is a positive relationship between higher socio-economic status and higher rates of RP. In California [5], socio-economically or educationally advantaged groups were less likely to be treated in compliance with guidelines, suggesting that patients who demand more or can afford more are increasingly likely to be treated, even when according to the guidelines they are considered unsuitable; an example is men aged >70 years [3,24]. In concurrence, our study also found a strong socio-economic effect, and although it was reduced in the fully adjusted models, this was mainly a result of the additional effect of private health insurance.

Tarman et al. [28] found that in an equal-access health system, patients from lower socio-economic groups were less likely to be treated in compliance with guidelines, suggesting that patients who demand more or can afford more are increasingly likely to be treated, even when according to the guidelines they are considered unsuitable; an example is men aged >70 years [3,24]. In concurrence, our study also found a strong socio-economic effect, and although it was reduced in the fully adjusted models, this was mainly a result of the additional effect of private health insurance.
Factors may also include less demand for surgery, surgeon preference and psychosocial reasons, e.g. fear of incontinence or impotence [29]. Men in higher socio-economic groups also tend to have a higher quality of life [30], which may affect treatment practices and survival [31].

Men first admitted to rural hospitals were much less likely to have RP and tended to have higher mortality. The mortality risk was confounded by each of the other factors of disadvantage, which may be indicative of more poverty in non-metropolitan areas and the lack of availability of private healthcare [31]. The rural and remote incidence of prostate cancer lagged behind that in metropolitan areas until 1996, reflecting lower PSA testing rates [2,31], and conceivably accounting for the lower treatment and survival rates. After adjusting for socio-demographic disadvantage, in the present study the case fatality in men with a first admission to a rural hospital was no different to that of men first admitted to metropolitan hospitals, who had a much higher use of RP. In this regard, ‘first admitted to a rural hospital’ is acting like an instrumental variable [32] and the result is consistent with no real effect of RP vs other treatment approaches on patient survival.

Related to hospital location was the residential location of the patient: men from remote areas tending to be admitted to metropolitan hospitals, whereas those from rural areas went to rural hospitals, thus explaining some of the fluctuation seen in the use of radical surgery and survival in the ARIA. Possibly rural patients are diagnosed at a later stage, are not given the choice of surgery, not recommended to undergo surgery, or rural surgeons choose not to use RP [6].

Radiotherapy options are also more limited in rural hospitals, making it unlikely that rural men are choosing radiotherapy rather than surgery, with the heavy commitment to travel to metropolitan centres for ongoing treatment [33]. Travelling distances to receive radiotherapy, even as little as 60 km, have been shown to affect treatment choices [34–36]. With 1.2 million people living in and around Perth, and the remaining WA population of 0.7 million people spread over 2.6 million km², travelling distance is a major barrier in accessing health services.

This study benefited from using population-based hospital morbidity records to examine surgical treatment patterns for prostate cancer in WA [10,22,23]. However, a limitation was that the data were not primarily collected for this purpose; in particular, outpatient radiotherapy treatment information was not collected. Furthermore, it was impossible to differentiate accurately if the inpatient radiotherapy was curative or palliative. In this study, patients who had radiotherapy with no surgery would have been categorized as having non-radical surgery, leading to an underestimate of active treatment patterns. It is plausible that the lower rates of RP found in WA were caused by men having radiotherapy rather than surgery, but the reduced survival rate in the groups not treated by RP does not concur with this scenario.

The lack of conclusive randomized control trials comparing approaches such as RP, radiotherapy and ‘watchful waiting’ limits the range of policy interventions that can realistically be considered. In WA, with vast distances and a widely spread population, sophisticated radiotherapy services are unlikely to be an option in non-metropolitan areas, whereas other options may be more applicable. With any of these options, identifying the disease at a stage amenable to curative treatment is still an issue. This suggests that while screening with PSA testing may not be accepted as per the guidelines [25], educating rural men and their GPs to recognize the symptoms earlier and test appropriately (e.g. not men aged ≥70 years) may be more important. The variability in treatment method and survival between metropolitan and rural patients suggests that policies to counteract this problem are required. This may either involve taking the surgeons and multidisciplinary team members to the rural areas, providing resources to surgeons already in rural areas, or bringing the rural patients to metropolitan areas. Men from remote areas will almost certainly continue to travel long distances, as there are too few to make visiting specialist services an economically viable proposition. Ensuring continuity of care with ongoing observation will be important in any scenario. Further research is required to determine whether lower rates of RP are a result of patient choice, are related to tumour stage or the result of medical attitudes; these factors could also affect any other active intervention.

Of considerable concern is the reduced rate of surgery and increased mortality in patients with no private health insurance or access to a private hospital, and in those in more socio-economically disadvantaged groups. As with rural men, the influence of PSA testing on the stage of the prostate cancer at diagnosis is a consideration, and patient and GP education in testing symptomatic men at an appropriate time may be required. While the present Australian government has adopted policies to support private health insurance [9], men in the lower socio-economic groups are unlikely to be able to purchase private health insurance [37]. Even if men in the public system are undergoing radiotherapy rather than RP the mortality rates in publicly treated men continue to be higher, which again may be indicative of stage at diagnosis or treatment pattern. The stage at presentation, ease of compliance with treatment options, especially radiotherapy, and costs to the patient and health system should be assessed and policies initiated to lower barriers.
In an uncertain climate, with no evidence for clinical practice guidelines and screening options, the way forward remains unclear, albeit that reducing inequalities in the Australian health system is fundamental to a health system which prides itself on universal coverage.

ACKNOWLEDGEMENTS

The authors sincerely thank the Western Australian Data Linkage Project for their assistance with the provision of data and advice for this research. This study was funded by an NHMRC postgraduate research scholarship.

CONFLICT OF INTEREST

None declared. Source of funding: National Health and Medical Research Council Post-Graduate Scholarship.

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Correspondence: Sonja E. Hall, School of Population Health, The University of Western Australia, 35 Stirling Highway, Crawley WA 6009, Australia. e-mail: shall@sph.uwa.edu.au

Abbreviations: RP, radical prostatectomy; WA, Western Australia; OR, odds ratio; RR, relative risk; ICD, International Classification of Diseases (code); IRSD, index of relative socio-economic disadvantage; ARIA, Accessibility/Remoteness Index of Australia.
The economic consequences of prostate and bladder cancer in the UK

VIJAY K. SANGAR*, NARASIMHAN RAGAVAN*, SHYAM S. MATANHELIA, MIKE W. WATSON and ROSIE A. BLADES

Department of Urology, Lancashire Teaching Hospitals NHS Trust, Preston, Lancashire, UK
*Joint first authors

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OBJECTIVE

To compare the costs of managing prostate and bladder cancer and relate them to current expenditure on research, as the increasing prevalence of both necessitates the adequate direction of resources.

METHODS

All new prostate and bladder cancers diagnosed in 2001–2002 were identified from British Association of Urological Surgeons Section of Oncology database (national and local). The total cost of diagnosing, treating and following patients for 5 years was estimated as the sum of direct costs (National Health Service) and indirect costs (loss of earnings). Annual research fund allocation (RFA) for each cancer were obtained from the National Cancer Research Institute UK.

RESULTS

There were 15,099 and 7,703 patients with newly diagnosed prostate (mean age 72.3 years) and bladder cancers (mean age 71.3 years). The total cost for prostate cancer was estimated at £92.74 million, with hormonal therapy alone costing £63.1 million. The total cost for bladder cancer was £55.39 million, of which superficial disease cost £35.25 million. The mean cost per patient was more for bladder than for prostate cancer (£63.49 vs. £72.94). The RFA allocation during this period was £20.56 million and £4.62 million for prostate and bladder cancer, respectively, and the respective RFA allotment per pound spent on the mean cost of disease management per patient was £2818 and £553.

CONCLUSION

Individual patient management is more costly for bladder cancer but less is invested in research than for prostate cancer. This study suggests a need to re-evaluate future strategies.

KEYWORDS

prostate cancer, bladder cancer, direct costs, indirect costs, total costs, research fund allocation

INTRODUCTION

Prostate and bladder cancer account for 85% of all genitourinary malignancies, with prostate cancer ranking first among all cancers and bladder cancer fifth [1]. In the UK during 1999, the incidence was 20,842 and 10,524 for prostate and bladder cancer, respectively [1]. The evidence suggests an increasing trend in the occurrence of both malignancies in recent years, with the incidence of these cancers being 18,201 and 10,287 in 1997 [2]. Nonetheless, better treatment methods and earlier detection has resulted in a decrease in cancer-related mortality [3], as shown by the age-standardized death rate per million population for prostate cancer, at 302 and 71.3 years). The corresponding values for male bladder cancer were 121 and 93 deaths per million.

Treatment for both diseases is well established but varies depending on the stage and grade. For localized prostate cancer the treatment options include active monitoring or watchful waiting, radical prostatectomy (RP), radical radiotherapy, and more recently brachytherapy. In advanced disease the options include hormone manipulation, with most patients receiving LHRH analogues. In addition, a few patients may undergo orchidectomy or may receive antiandrogen therapy. In those with hormone-refractory disease second-line hormone therapy is used and includes the addition of antiandrogens or oestrogens. Chemotherapy for advanced prostate cancer is used in a few patients, and in those with known bone involvement who complain of pain, analgesia is the primary treatment, followed by local radiotherapy. However bisphosphonates may be recommended in a selected few, to prevent bone disease-related complications.

For superficial bladder cancer the treatment involves endoscopic surveillance, tumour resection and intravesical chemotherapy. Those with locally advanced bladder cancer may have radical surgery or radiotherapy, whilst metastatic disease is treated essentially with chemotherapy.

Once treated, all patients require some form of follow-up, as there is a significant risk of recurrence. The progression rate for prostate cancer varies with the grade of the disease, at 15–52% [4]. More than 60% of superficial bladder cancers will recur despite treatment, whilst the risk increases with the grade of the disease [5,6]. Furthermore, the cited mortality rates show that significantly many patients survive, thus resulting in an accumulation of patients requiring continuing care.

There is no doubt that the diagnosis, treatment and follow-up of these two malignancies result in a significant burden on National Health Service (NHS) resources. However, there are limited data available on the economic impacts of prostate and bladder cancer. Chamberlain et al. [7] suggested that the cost of prostate cancer was at least £45 million annually. However, this value was based on incidence and prevalence data from the early 1990s, and only accounted for primary-care costs and the cost of in-patient days. At that time there were no national statistics available for the cost of radiotherapy, surgery, hormone therapy and...
chemotherapy, and hence the estimates were grossly underestimated.

It is paramount that accurate data are available with which to plan future resource allocation and to highlight areas where more cost-effective management is required. The aims of the present study were to assess the impact of prostate and bladder cancer on the UK healthcare and social economy. We present the direct (DC) and indirect costs (IC) of diagnosis, treatment and 5-year follow-up of all patients diagnosed with prostate and bladder cancer in the UK during 2001–2002, and total costs (TC) and cost per patient, with comparisons between the cancers and correlations with current research expenditure.

**METHOD**

All new prostate and bladder cancers diagnosed between January 2001 and 2002 were identified from the BAUS Section of Oncology database [8]. For comparison, patients with the same diagnosis at our Institute in an equivalent period were also identified from the local BAUS database.

The DC were defined as the expenditure related to the diagnosis, treatment and 5-year follow-up of the patients identified. This included outpatient visits, haematological, biochemical, pathological, microbiological and radiological investigations required during diagnosis and follow-up, as well as the costs of various treatments (surgery, radiotherapy, chemotherapy, hormone therapy and immunotherapy). The protocols for the investigation of patients during diagnosis and follow-up were based on European Association of Urology guidelines [9,10]. The individual costs of these investigations were obtained from the local NHS Trust Finance Directorate and are thought to be typical of most Trusts across the UK. The patients were divided into various subgroups according to the stage of disease and treatment. The DC were calculated for each subgroup of patients and summed.

The IC were defined as loss of earnings based on the average weekly wage in relation to age and sex for the year 2000 (Table 1), the data for which were obtained from the UK Economics Database [11]. Loss of earnings was defined as any activity related to diagnosis, treatment and follow-up that required time off from normal employment.

The details available from BAUS database were insufficient to calculate the IC, as there were no details of the age and sex distribution in the individual subgroups. Hence, for the purpose of calculating IC, the cohort of patients who were diagnosed with prostate and bladder cancer at our institute during the same period were used and costs extrapolated to the national data (Table 2). The treatments received by individuals dictate the follow-up, which in turn affects costs, and hence local and national data were compared for the number of patients receiving particular treatments (Table 3).

The TC of diagnosing, treating and following patients for 5 years were estimated as the sum of DC (NHS) and IC. The cost per patient was calculated as TC for each cancer divided by the incidence for each cancer. All calculations were based on the assumption that there would be no mortality or disease recurrence in any of these patients over the 5-year follow-up. The annual research fund allocation (RFA) for each cancer were obtained from National Cancer Research Institute (NCRI) [12].

**RESULTS**

In the period assessed there were 15,099 newly diagnosed prostate cancers (mean age 72.3 years; Table 2). The treatments for these patients were RP (1506), radical radiotherapy (2735), hormone therapy (7127) and chemotherapy (18). There were 1320 patients for whom no treatment was available from the database, so they were assumed to be on active monitoring. A further group of patients were identified in whom it was not clear, for

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**TABLE 1 The mean weekly earnings in 2000 (UK Economics Database 2002)**

<table>
<thead>
<tr>
<th>Age group, years</th>
<th>Mean weekly earnings, £</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
</tr>
<tr>
<td>&lt;18</td>
<td>151.3</td>
</tr>
<tr>
<td>18–20</td>
<td>217.2</td>
</tr>
<tr>
<td>21–24</td>
<td>314.7</td>
</tr>
<tr>
<td>25–29</td>
<td>390.1</td>
</tr>
<tr>
<td>30–39</td>
<td>479.8</td>
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<tr>
<td>40–49</td>
<td>520.7</td>
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<tr>
<td>50–59</td>
<td>491.8</td>
</tr>
<tr>
<td>60–64</td>
<td>407.4</td>
</tr>
</tbody>
</table>

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**TABLE 2**

<table>
<thead>
<tr>
<th>Category</th>
<th>Local (%)</th>
<th>UK (%)</th>
<th>TC (£M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hormones</td>
<td>42.1</td>
<td>47.2</td>
<td>63.1</td>
</tr>
<tr>
<td>Watchful waiting</td>
<td>10</td>
<td>8.7</td>
<td>1.8</td>
</tr>
<tr>
<td>RP</td>
<td>14.2</td>
<td>9.9</td>
<td>12.5</td>
</tr>
<tr>
<td>Radical radiotherapy</td>
<td>26.2</td>
<td>18.1</td>
<td>12.4</td>
</tr>
<tr>
<td>with hormones</td>
<td>7.1</td>
<td>–</td>
<td>(1.9)</td>
</tr>
<tr>
<td>(TURP*)</td>
<td>–</td>
<td>–</td>
<td>(0.02)</td>
</tr>
<tr>
<td>[Chemotherapy*]</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Bladder cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TURBT (low-grade)</td>
<td>56</td>
<td>60.3</td>
<td>35.2†</td>
</tr>
<tr>
<td>TURBT (high-grade)</td>
<td>16</td>
<td>10.2</td>
<td>6.1†</td>
</tr>
<tr>
<td>Cystectomy/related surgery</td>
<td>17.33</td>
<td>5.2</td>
<td>3.6</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>6.6</td>
<td>9.02</td>
<td>8.1</td>
</tr>
<tr>
<td>Systemic chemotherapy</td>
<td>2.6</td>
<td>1.1</td>
<td>1.5</td>
</tr>
</tbody>
</table>

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**TABLE 3**

<table>
<thead>
<tr>
<th>Category</th>
<th>Local (%)</th>
<th>UK (%)</th>
<th>TC (£M)</th>
</tr>
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<tr>
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<td>10</td>
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<td>1.8</td>
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<tr>
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<td>9.9</td>
<td>12.5</td>
</tr>
<tr>
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<td>26.2</td>
<td>18.1</td>
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</tr>
<tr>
<td>with hormones</td>
<td>7.1</td>
<td>–</td>
<td>(1.9)</td>
</tr>
<tr>
<td>(TURP*)</td>
<td>–</td>
<td>–</td>
<td>(0.02)</td>
</tr>
<tr>
<td>Bladder cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TURBT (low-grade)</td>
<td>56</td>
<td>60.3</td>
<td>35.2†</td>
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<tr>
<td>TURBT (high-grade)</td>
<td>16</td>
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<tr>
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<td>3.6</td>
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<td>8.1</td>
</tr>
<tr>
<td>Systemic chemotherapy</td>
<td>2.6</td>
<td>1.1</td>
<td>1.5</td>
</tr>
</tbody>
</table>

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*In the national data for prostate cancer, 1328 patients had TURP and 18 had chemotherapy. † With costs of mitomycin and BCG instillation.
cost calculations, what kind of treatment they received. These 1065 patients were entirely excluded from the calculation (organ-conserving surgery 12, other surgery 637, other treatments 396, immunotherapy three, and intravesical chemotherapy 17). There were 1328 patients who had a TURP and had a diagnosis of prostate cancer. For these patients the cost of diagnosis was calculated and included in the TC. However, the treatments for these patients were not available and therefore this value was excluded from the cost calculation.

During the period assessed there were 7703 newly diagnosed bladder cancers (mean age 71.3 years), with the disease being almost three times more common in men than women. Superficial disease was almost three times more common than invasive disease. Amongst these patients the treatment was not stated in 732, whilst in 337 the treatment was not clear enough to calculate cost (other surgery 157, systemic immunotherapy 40, hormones 26, other treatment 114). All these patients were excluded. Hence the cost calculation was based on 6634 patients, comprising transurethral resection of bladder tumour (TURBT) low-grade 4645, high-grade 794; radical radiotherapy, 695; radical cystectomy, 408; systemic chemotherapy, 92.

The TC for the diagnosis, treatment and 5-year follow-up of patients with prostate cancer diagnosed during 2001–2 was estimated at £92.74 million. Hormonal therapy was estimated to cost £63.1 million, thereby accounting for over two-thirds of the TC. The TC of radical radiotherapy and RP were similar, but almost 1.5 times more patients were treated with radical radiotherapy than with RP.

The TC for the diagnosis, treatment and 5-year follow-up of patients with bladder cancer diagnosed during 2001–2 was £55.39 million; the TC of superficial disease was £35.25 million, whilst the corresponding TC for invasive disease was £20.2 million. The TC for patients undergoing radical radiotherapy was over twice that for cystectomy (£8.1 vs £3.6 million). However, more patients were treated with radiotherapy than cystectomy (695 vs 408).

The percentage of patients receiving each treatment locally compared reasonably with national values (Table 2). In some instances more patients received radical treatment locally than nationally. However, local data were used for calculating IC in the proportion of patients in the pre-retirement age group only, and this accounts for a small proportion of TC. The DC form the greater proportion of the TC (90–98%) for both cancers (Table 4); DC implies that the burden is directly borne by the NHS.

Prostate cancer has a greater impact on the UK health economy than bladder cancer (£92.74 vs £55.39 million) (Table 5), because the incidence of the former is almost twice that of the latter (15099 vs 7703). However, the mean cost of treatment of each patient with bladder cancer is more than that for each patient with prostate cancer (£8349.2 vs £7294.2).

The annual RFA during 2001–2 as reported by the NCRI was £20.56 and £4.62 million for prostate and bladder cancer, respectively (Table 5) [12]. To compare these values according to the economic impact of each disease we calculated the RFA per pound spent on the mean cost of disease management per patient. This showed that £2818 is spent on the research of prostate cancer per pound spent on the cost of management per patient, whilst the corresponding value for bladder cancer was £553 (Table 5). This shows that investment in research for prostate cancer is five times greater than that for bladder cancer.

**TABLE 5 National expenditure for patients with prostate and bladder cancer diagnosed in 2001–2, and the RFA (based on NCRI values) as the total and against the cost of disease management per patient**

<table>
<thead>
<tr>
<th>Costs</th>
<th>Prostate</th>
<th>Bladder</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of TC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DC</td>
<td>97.6</td>
<td>94.5</td>
</tr>
<tr>
<td>IC</td>
<td>2.4</td>
<td>5.5</td>
</tr>
<tr>
<td>£ million:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TC</td>
<td>92.74</td>
<td>55.39</td>
</tr>
<tr>
<td>Estimated DC for NHS</td>
<td>90.5</td>
<td>33.97</td>
</tr>
<tr>
<td>IC</td>
<td>2.23</td>
<td>1.98</td>
</tr>
<tr>
<td>Cost of management/patient (£)</td>
<td>7294.2</td>
<td>8349.2</td>
</tr>
<tr>
<td>RFA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2001–02 (£ million)</td>
<td>20.56</td>
<td>4.62</td>
</tr>
<tr>
<td>disease management (£)</td>
<td>2818</td>
<td>553.34</td>
</tr>
</tbody>
</table>

**TABLE 4 Distribution of DC and IC for prostate and bladder cancers diagnosed in 2001–2 for the subsequent 5 years**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>92.74</td>
<td>94.5</td>
<td>99.4</td>
<td>99.8</td>
<td>99.2</td>
<td>99.3</td>
</tr>
<tr>
<td>Bladder</td>
<td>55.39</td>
<td>55.9</td>
<td>56.8</td>
<td>57.8</td>
<td>57.1</td>
<td>57.5</td>
</tr>
</tbody>
</table>

**DISCUSSION**

Prostate and bladder cancer are the commonest malignancies treated by urologists. The strategies involved in the diagnosis, treatment and follow-up of both are well investigated, but the cause and prevention are to some degree relatively less well explained. Healthcare systems should ideally function to provide the optimum care regardless of cost. However, the definition of optimum care is debatable and unfortunately the cost of treatment is a real issue in medicine worldwide. In the UK there are few data on the cost of treatments for prostate and bladder cancer, and this is likely to be related to the difficulty in calculating such values, which involve many variables. However, these data are most important in planning future urological healthcare investment strategies. The present study is one of the first to assess the economic burden of prostate and bladder cancer in the UK.

Presently, the estimated TC, over a 5-year period, of managing patients with prostate cancer diagnosed in one calendar year (2001–2) is £92.8 million, whilst that for bladder cancer in the same period is £55.39 million, thus showing that both diseases are relatively costly to the UK health economy.

The present study only estimated the economic impact of these two cancers; we
consider that the calculations are underestimates of the true expenditure for several reasons. First, there is the inadequacy of recording the incidence of both tumours, and their various treatments, in the BAUS database. This resulted in the exclusion of some patients and therefore an underestimate of the costs. Second, the IC were calculated only for those patients who were in the employment age group. The drawback of this is that patients who were designated as having retired realistically still contribute to the economy, and furthermore many still may be in some form of employment. A more accurate assessment of IC could have been obtained by using values for 'present value of lifetime earnings', which considers that those retired still have a value to the economy, regardless of whether they are employed. However, such figures are not available for the UK. Third, it was assumed that there was no disease recurrence or mortality during the 5-year follow-up. This assumption was made for ease of calculations, but including this would undoubtedly increase the costs further. In addition, no weight was given in our calculations to the expenditure related to palliative care, nursing homes or social services, whilst there can be no possible estimate of the cost for the amount of mental and physical suffering that patients and their relatives undergo. Last, the values stated represent the cost of managing a group of patients diagnosed in one calendar year, over a period of 5 years. Realistically there would be a gradual accumulation of patients over time, which would increase costs further.

In the treatment of prostate cancer the expenditure on hormone manipulation contributes ¬68% of the TC, almost entirely from the use of LHRH agonists, which currently are the mainstay of hormone therapy. Orchidectomy is comparable with LHRH agonist therapy both in terms of treatment efficacy and in maintaining the quality of life of patients [13–16], and is undoubtedly the least expensive. This would suggest that offering patients orchidectomy should be considered for all those treated with hormone manipulation.

The overall costs of RP and radiotherapy for prostate cancer are comparable, although more patients were treated with radiotherapy. The number of patients opting for specific treatments is variable, as in most cases it will be dictated by patient preference and the availability of local skills and resources. The cost per patient treated by radiotherapy was considerably cheaper than by RP for early prostate cancer in the present assessment, and comparable with previous assessments [17].

Some patients in the present study were diagnosed with prostate cancer from the histology of specimens taken at TURP for BOO. The cost of TURP was included as part of the cost of diagnosis. Specific data on the treatment offered to these patients was not available and therefore could not be calculated. The present study aimed to provide as realistic a view as possible and therefore included the available data in the TC for prostate cancer; excluding TURP gave an overall cost reduced by £1.95 million, to a TC of £92.73 million.

In comparison to the study by Chamberlain et al. [7] on the cost of prostate cancer, the current values may initially seem to be an underestimate. There are several reasons for this; Chamberlain et al. based their values on incidence and prevalence data from the early 1990s, obtained from primary care and cancer registry sources which may not have been accurate. In addition, they concentrated on inpatient stay, primary care and community care costs. At that time there were no data available on the costs of treatments such as radiotherapy. The current study estimated costs of secondary care, main therapies and loss of earnings over a 5-year period in a cohort of patients diagnosed in one calendar year. Hence the values differed, as they measure different variables in different populations.

The TC of bladder cancer is less than for prostate cancer, reflecting that the incidence of the former is half that of the latter. However, the cost of management per patient is greater than for prostate cancer (Table 5), probably because patients with bladder cancer are followed using a protocol that involves regular cystoscopies and general anaesthetics. The current study estimated costs of secondary care, main therapies and loss of earnings over a 5-year period in a cohort of patients diagnosed in one calendar year. Hence the values differed, as they measure different variables in different populations.

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The costs of bladder cancer management could be reduced in several ways, e.g. allowing less frequent check cystoscopies in superficial low-grade disease, which is a relatively benign condition, and considering outpatient rather than inpatient general anaesthetic cystoscopy [18]. Considering cheaper and less-invasive surveillance is, as yet, not an option, but new urinary tumour markers, once available, may increase the accuracy of predicting tumour recurrence, and if widespread use ensures this may relate to a cost saving. In addition, the search for better intravesical therapies may eventually lead to far less recurrence and progression of the disease.

The treatment of high-grade and invasive disease is variable, and includes endoscopic resections, radical cystectomy and radiotherapy, with the judicious use of intravesical chemo- and immunotherapy. In the current estimates, radical radiotherapy was more expensive than cystectomy, possibly because more patients were treated by this method, but that such patients still need to undergo regular cystoscopic review is also important.

In the UK, ¬£450 million is spent on research every year, of which most is provided by 15 major bodies (¬£335 million) [12]. The NCRI
incorporates the data from these major funding organizations, and being the major funding network it is assumed that the data should reflect the research spending by the nation as a whole. The annual RFA for various cancers obtained from NCRI database shows that investment in prostate cancer research was over £20 million, whilst for bladder cancer it was <£5 million. Comparing these values to the cost of disease, prostate cancer had an investment of £2818 for every pound spent on disease management per patient, compared to £533 for bladder cancer. This vast difference undoubtedly and rightly relates to the incidence and mortality of each disease. However, the present study highlights that on an economic basis there are certain areas in both cancers where more investment might lead to more efficient management and reduced cost. The NCRI data cannot be used to identify the specific areas of research in which investment is made; it is likely that most is directed towards diagnosis and treatment, despite that in the longer term the only realistic gains may lie in understanding the cause of the disease and in producing prevention strategies.

In the future the costs of managing these two diseases are likely to increase as a result of several factors, e.g. increasing incidence, increasing public awareness, the widespread use of PSA testing, the possible introduction of PSA screening, the availability of newer use of PSA testing, the possible introduction of preventive management of clinically localized prostate cancer. N Engl J Med 1994; 330: 242–8
8 BAUS. Analyses of minimum data set for urological cancers. London: BAUS Section of Oncology, October 2002

Correspondence: Narasimhan Ragavan, Department of Urology, Royal Preston Hospital, Preston PR2 9HT, UK.
e-mail: n.ragavan@lancaster.ac.uk

Abbreviations: RP, radical prostatectomy; NHS, National Health Service; TC, total costs; IC, indirect costs; DC, direct costs; RFA, research fund allocation; NCRI, National Cancer Research Institute; TURBT, transurethral resection of bladder tumour.
Parenchymal imaging adds diagnostic utility in evaluating haematuria

JAY S. BELANI, AAMER FAROOKI*, SRINIVASA PRASAD*, YAN YAN, JAY P. HEIKEN* and ADAM S. KIBEL
Division of Urology and *Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, Missouri, USA
Accepted for publication 1 September 2004

OBJECTIVE
To compare the findings of renal ultrasonography (US) in the evaluation of patients with and with no haematuria. The increased use of cross-sectional imaging and US has led to a dramatic improvement in the diagnosis of renal masses, such that computed tomography and/or US have been integrated into the diagnostic evaluation of haematuria, and many more incidental renal lesions are now detected. Thus it is possible that the lesions identified during evaluation for haematuria are incidental, i.e. identified serendipitously, and unrelated to the haematuria.

PATIENTS AND METHODS
We retrospectively compared the US findings obtained from 301 patients referred for new-onset haematuria to those obtained from 600 patients being evaluated for other than urological reasons. All imaging and patient charts were reviewed to verify the clinical and radiological data.

RESULTS
Haematuria was associated with all renal abnormalities, with an odds ratio (OR, 95% confidence interval) of 4.7 (3.6–7.3). Importantly, haematuria was associated with a renal mass, with an OR of 6.7 (2.8–16.3). Subset analysis revealed that patients with macroscopic and microscopic haematuria had significantly more renal abnormalities (OR 4.7, 2.7–8.2, and 5.3, 3.2–8.8, respectively) and renal masses (OR 7.3, 2.7–20.3, and 6.5, 2.3–18.6, respectively) than controls.

CONCLUSIONS
Both macroscopic and microscopic haematuria are associated with a greater risk of identifying renal lesions. This supports the conclusion that the renal lesions identified with modern imaging techniques during the evaluation of both microscopic and macroscopic haematuria are not serendipitous.

KEYWORDS
ultrasonography, haematuria, renal lesions, incidental

INTRODUCTION
Haematuria, both macroscopic and microscopic, is common in urological practice and may be the only evidence of urological malignancy. Therefore, most physicians agree that it warrants a thorough evaluation [1]. Macroscopic haematuria is clearly a risk factor for upper tract pathology. Up to 30% of patients with macroscopic haematuria have an upper tract cause, and 1–6% have an upper tract malignancy [2–4]. Moreover, as many as 38% of patients with RCC present with gross haematuria [5].

Microscopic haematuria is also clearly a risk factor for upper tract disease; it has a prevalence of 2.5–4% in a screening population of healthy, asymptomatic individuals [6,7]. Although the evaluation is not positive as often as for macroscopic haematuria, 13% of patients will have an upper tract cause and 0.4–0.7% will have a malignancy [2,3].

Haematuria can be caused by pathology at any point along the urinary tract, hence all patients are evaluated with cystourethroscopy and upper tract imaging. Classical upper tract imaging has been IVU with plain films. However, studies have shown that IVU alone may miss significant upper tract lesions, particularly renal masses [2,8]. Therefore, CT or ultrasonography (US) have been gradually integrated into the evaluation of haematuria [2,9]. While CT and US clearly provide better renal parenchymal imaging and diagnose additional upper tract tumours, it is unclear if the renal pathology identified during an evaluation for haematuria is truly the cause of the haematuria. Lesions identified are often small and peripheral, and therefore possibly not the cause of the haematuria. The lesions may simply be recognized serendipitously.

To answer this question we conducted a case-control study to determine if significant renal pathology is more common in patients being evaluated for haematuria. The results of renal US obtained while evaluating new-onset haematuria were compared to those obtained for other than urological reasons, to determine if the findings on renal US were serendipitous. In addition, to determine if US provided added utility, in patients with positive findings on US we reviewed other imaging methods (IVU, CT, MRI) used in the evaluation.

PATIENTS AND METHODS
We identified 301 patients referred to our clinic over a 10-month period for new-onset haematuria and who had US as part of their evaluation; the assessment was individualized by surgeon preference, and may have included (but was not limited to) IVU, cross-sectional imaging (CSI), urine cytology, urine culture and cysto-urethroscopy. Each patient’s chart was reviewed to verify the clinical and radiological data.

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haematuria was macroscopic or microscopic. All imaging was reviewed again to confirm the original findings. Macroscopic haematuria was defined as frank bloody urine, and microscopic haematuria as more than five red blood cells per high-power field on microscopic analysis, with no history of macroscopic haematuria.

As a control cohort we retrospectively reviewed all US examinations obtained over a 3-month period at our institution, identifying 600 renal US studies for other than urological reasons (including haematuria), e.g. cholecystitis, hernias and hepatitis. Standard practice at our hospital is for all patients to have both kidneys evaluated in any abdominal US. All US studies were reviewed again to confirm the original findings. All patients who had a renal transplant were excluded from both the patient and control arms of the study. Institutional Review Board approval was obtained before chart review or review of imaging.

Each lesion found by parenchymal imaging was grouped into a renal or nonrenal mass abnormality. Renal masses included renal neoplasms, RCC, upper tract TCC, complex renal cyst or angiomyolipoma (AML). Nonrenal mass abnormalities included any hydronephrosis, renal calculi, medical renal disease or any other deviation from normal.

In an effort to assess the utility of other imaging, we identified all additional imaging studies (IVU, MRI, CT) obtained as part of the patient’s haematuria evaluation or to further define the abnormality identified on US. All films were reviewed again to ensure the accuracy of the diagnosis. Pathology reports of patients who required operative intervention were reviewed.

All data were evaluated using multivariate regression analysis to control for confounding factors, with the chi-square test used to test statistical significance and the odds ratio (OR) to quantify the strength of association.

**RESULTS**

The 301 patients with new-onset haematuria comprised 161 females and 140 males (mean age 58 years, range 16–93); 129 had macroscopic and 133 microscopic haematuria, but on reviewing the charts of 39 patients with haematuria, the TCC of the renal pelvis was followed with serial imaging. Of patients with haematuria, the RCC of the renal pelvis was 8 cm and the three RCCs 5.5, 3 and 2 cm (mean 3.3). The patient with the TCC died from subdural haematoma before surgical resection. The patient with the 5.5 cm lesion had widespread metastatic disease. The 3 cm renal mass was excised via a laparoscopic radical nephrectomy and was a clear-cell RCC.

In the control patients all three renal neoplasms were suspected RCC; they measured 3, 3 and 1 cm (mean 2.3). One patient died from comorbid conditions, one refused surgical intervention because of his advanced age and the patient with the 1 cm lesion was followed with serial imaging. Of the four patients with AMLs, each lesion measured ≤1 cm and all patients were followed with serial imaging. Of patients with haematuria, the RCCs were 5.5, 3 and 2 cm (mean 3.3). The patient with the RCC died from subdural haematomata before surgical resection. The patient with the 5.5 cm lesion had widespread metastatic disease. The 3 cm renal mass was excised via a laparoscopic radical nephrectomy and was a clear-cell RCC. Finally, the 2 cm lesion was followed with serial imaging because of the patient’s significant cardiac comorbidities. All six AMLs were ≤1.4 cm and managed conservatively. Of the nine patients with complex renal cysts, seven had Bosniak II and were followed conservatively, and two had Bosniak III cysts. One of these patients refused surgical intervention.

The 600 controls comprised 411 women and 189 men (mean age 58 years, range 16–93); 129 had macroscopic and 133 microscopic haematuria. In the control patients all three renal masses (four complex renal cysts, one RCC, one TCC and three AMLs) and 21 had other renal abnormalities; among the 133 with microscopic haematuria, eight had renal masses (three complex renal cysts, two RCCs and three AMLs), and 27 had other renal abnormalities. Among the 39 patients whose haematuria was not categorized, two had a complex renal cyst and six had other renal abnormalities.

Because age and gender were significantly different between study and control patients, a multivariate regression analysis was used to control for these variables. The OR for all abnormalities, nonrenal abnormalities, and renal masses remained statistically significant for patients with macroscopic and microscopic haematuria (Table 1). The ORs of macroscopic and microscopic haematuria for finding a renal mass (7.3 vs. 6.5) were not significantly different (P = 0.05).

**TABLE 1** Comparison of controls to all patients with haematuria, or microscopic vs macroscopic, controlling for differences in age and gender

<table>
<thead>
<tr>
<th>Group</th>
<th>Findings on US</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All abnormal</td>
<td>Non-renal mass</td>
<td>Renal mass</td>
</tr>
<tr>
<td>Controls</td>
<td>36 (6.0)</td>
<td>29 (4.8)</td>
<td>7 (1.2)</td>
</tr>
<tr>
<td>Haematuria</td>
<td>73 (24.3)</td>
<td>54 (18)</td>
<td>19 (6.3)</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>4.7 (3.6–7.3)</td>
<td>4.6 (2.9–7.5)</td>
<td>6.7 (2.8–16.3)</td>
</tr>
<tr>
<td>Macroscopic</td>
<td>30 (23.3)</td>
<td>21 (16.3)</td>
<td>9 (7.0)</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>4.7 (2.7–8.2)</td>
<td>4.1 (2.3–7.5)</td>
<td>7.3 (2.7–20.3)</td>
</tr>
<tr>
<td>Microscopic</td>
<td>35 (26.3)</td>
<td>27 (20.3)</td>
<td>8 (6.0)</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>5.3 (3.2–8.8)</td>
<td>5.4 (3.0–9.4)</td>
<td>6.5 (2.3–18.6)</td>
</tr>
</tbody>
</table>

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65
Of the 19 patients with haematuria who had renal masses, 14 also had an IVU with tomograms in their evaluation. IVU showed one of the complex renal cysts but did not detect any of the RCCs or AMLs. Ten of the 19 patients had either CT or MRI to further evaluate the renal abnormality. All 10 US findings were verified by CT or MRI (Table 2).

**DISCUSSION**

The classical evaluation for haematuria for many years included cytology, urine culture, cystoscopy and IVU. Because of concern about missing parenchymal lesions, additional imaging is also often obtained. This parenchymal imaging, usually US or CT, clearly identifies additional lesions. However, as it has been well documented that incidental renal masses are commonly detected as part of routine imaging [10,11], it is unclear if the lesions found are being identified as a result of the haematuria or are simply serendipitous.

A recent meta-analysis of five series of screening CT consisting of 16174 patients showed that the rate of detection of RCC was 0.11–0.75% [12]. The present data suggest that in a screening population with no urological disease, 1.2% of patients will have a renal mass abnormality on parenchymal imaging and 0.5% will have a lesion suspicious for a renal neoplasm.

In the present patients being evaluated for haematuria, US identified clinically significant renal abnormalities beyond what would be expected serendipitously. This was true for patients who presented with either macroscopic or microscopic haematuria. Of particular importance, the risk of identifying renal parenchymal abnormalities, which require follow-up or intervention, was 6.7 times higher for patients with haematuria, 7.3 times higher for those with macroscopic and 6.5 times higher for those with microscopic haematuria. Moreover, there was no statistically significant difference between the ORs for the groups with macroscopic or microscopic haematuria. Hence, the extent of haematuria does not seem to affect the likelihood of finding a renal mass abnormality.

Previous prospective studies showed clearly that IVU fails to detect many upper tract lesions. In the study by Khadra et al. [2], IVU failed to identify 21% of renal tumours found on US; thus they concluded that renal US is an important adjunct to IVU in evaluating patients with macroscopic haematuria. Recently, CT has been increasingly used to replace IVU when evaluating haematuria, as it provides more information than IVU [8,9]. CT has been shown to be more effective in detecting parenchymal lesions, nephrolithiasis and vascular anomalies that can explain the haematuria [8,9]. Gray-Sears et al. [8] showed that CT had a greater specificity, sensitivity and accuracy in detecting urological pathology, and resulted in less additional radiography to confirm the diagnosis, than if IVU were used initially. Lang et al. [13] diagnosed an additional 20 renal neoplasms using CT urography among 600 patients who had a negative evaluation for haematuria, using a standard protocol. While these three prospective trials all show clearly that parenchymal imaging increases the diagnosis of renal abnormalities, they do not confirm that the renal lesions are the cause of the haematuria; the present findings support this conclusion. Both macroscopic and microscopic haematuria were clearly associated with an increased risk of renal parenchymal lesions.

Most would agree that for patients with macroscopic haematuria, both parenchymal and adequate collecting-system imaging are important to exclude a mass causing the haematuria. Studies have shown that 3% of patients with macroscopic haematuria will have a renal cancer as the cause [3]. The present data suggest that 7% of patients with gross haematuria will have renal masses and 1.5% will have renal cell cancer. Parenchymal imaging is clearly important for patients with macroscopic haematuria, with an OR of 7.3 (P < 0.001) for finding significant renal abnormalities compared to controls. Importantly, these lesions may not be detected by IVU.

For patients with microscopic haematuria there are no published statistical reports that assess the role of IVU, US, CT or MRI [9]. In a meta-analysis of 1689 patients [3], only 0.5% of those with microscopic haematuria were found to have renal tumours, implying that parenchymal imaging is of little value. However, Grossfeld and Carroll [1] argued that microscopic haematuria warrants evaluation, given that upper tract malignancy can cause serious morbidity or mortality; the present data support this contention. Parenchymal imaging is 6.5 times more likely to find serious disease that may require surgical intervention than in controls.

Importantly, the present study was not designed to assess the relative utility of IVU, US or CT, but simply to determine if the lesions identified with parenchymal imaging were truly associated with the haematuria. However, US identified three renal cancers that would have been missed by IVU. In addition, the data suggest that CT is better than IVU in detecting parenchymal abnormalities; CT showed all the abnormalities discovered by US, whereas IVU detected only 7.1% of the lesions.

The present data support the contention that parenchymal imaging not only identifies more renal abnormalities but that these lesions are caused by the haematuria. Therefore parenchymal imaging is important for evaluating patients with haematuria. Whether CT urography or IVU combined with US is more cost-effective and accurate is still in question, and requires further study.

Although we found that US provides additional value in evaluating haematuria the study has several limitations. First, it is a retrospective analysis, and we could not determine whether haematuria was microscopic or macroscopic in 39 patients. Second, we did not assess the sensitivity or specificity of US, as we could not evaluate what diagnoses were missed by it. Last, we had to use multiple regression models to control for differences in age and gender between the study and control groups.
In conclusion, US is more likely to detect renal parenchymal masses in patients with haematuria than in a control population. Therefore, renal masses detected as a result of screening are not serendipitous discoveries, but are truly associated with the haematuria, either macroscopic or microscopic. Whether the combination of IVU and US is superior to CT urography is still in question and requires further study.

CONFLICT OF INTEREST

None declared.

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Correspondence: Adam S. Kibel, Division of Urologic Surgery, Washington University School of Medicine, 4960 Children’s Place Campus, Box 8242, St Louis, MO 63110, USA. e-mail: kib ela@msnotes.wustl.edu

Abbreviations: US, ultrasonography; AML, angiomyolipoma; CSI, cross-sectional imaging; OR, odds ratio.
Comparison of bipolar transurethral resection of the prostate with standard transurethral prostatectomy: shorter stay, earlier catheter removal and fewer complications

JONATHAN S. STARKMAN and RICHARD A. SANTUCCI
Department of Urology, Wayne State University School of Medicine, Detroit, Michigan, USA
Accepted for publication 21 September 2004

OBJECTIVE
To assess bipolar transurethral prostatectomy (TURP) using the Gyrus system (Gyrus Medical, Maple Grove, MD) compared with a standard monopolar TURP.

PATIENTS AND METHODS
All 43 patients undergoing TURP from November 2000 to August 2002 were reviewed retrospectively; the 1.5-year observation period allowed for the detection of late complications. In all, 18 consecutive patients had standard and 25 had bipolar TURP.

RESULTS
The resection was 18 g for standard and 15 g for the Gyrus TURP (part of the Gyrus chips are vaporized during resection). The Foley catheter was removed sooner (1.8 vs 3.2 days) and the hospital stay was less in the Gyrus group (1.2 vs 2.1 days). Acute complications occurred in a third of the standard group and four (16%) of the Gyrus group. Long-term complications were comparable, at two each in the standard and Gyrus groups. Four patients (15%) with small glands went home on the day of surgery, needing no bladder irrigation after Gyrus TURP.

CONCLUSION
Few innovations in TURP technique have been described in the past few decades but comparing Gyrus to standard TURP showed that the former allows earlier removal of the urinary catheter and earlier discharge from hospital, while decreasing complications. The Gyrus system also has other benefits; it allows coagulation of tissue during resection, resulting in excellent intraoperative visualization, and normal saline is used as the irrigant fluid, reducing the potential for TUR syndrome. The shorter stay after Gyrus TURP can result in cost savings of up to $1200/patient/day at our institution.

KEYWORDS
transurethral resection of prostate, Gyrus, bipolar
with the active and return electrode on the same axis (axipolar) separated by a ceramic insulator [7]. TURP was conducted according to the well described principles of endoscopic electrosurgery [9,10]. Most patients were admitted after surgery for continuous bladder irrigation (CBI) and observation. CBI was continued until the urine was clear, typically within 24 h after surgery. The catheter was removed if the urine was clear in the absence of irrigation, and the patient was then given a voiding trial and discharged home if voiding spontaneously.

Results were analysed for length of hospital stay, catheterization, complications during and after TURP, and weight of tissue resected. Patients were observed during a 1.5-year follow-up to allow for the detection of late complications. Results were assessed statistically using Student’s t-test.

RESULTS

The mean (range) age in the standard and bipolar TURP groups was 65 (41–82) and 65 (48–81) years, respectively; the respective mean size of prostatic resection was 18 g and 15 g (according to Gyrus Medical, up to 5% of the resected prostatic tissue is vaporized during the procedure and not available for pathological analysis). The respective duration of catheterization was 3.2 (1–15) and 1.8 (1–5) days ($P=0.12$) and the hospital stay 2.1 (1–7) and 1.2 (0–5) days ($P=0.11$). One patient in the Gyrus group was excluded from the catheterization analysis, as he had direct internal visual urethrotomy of two bulbar urethral strictures at the same time as his TURP. His catheter was left indwelling for 5 days to comply with the standards of treatment after such urethrotomy, and was removed without sequelae in the office.

Four of 26 (15%) patients were discharged home on the day of surgery after bipolar TURP, as they required no CBI. These patients had the catheter removed on the following day in the office; all these patients had relatively small resections (5, 5 and 10 g) and had clear urine in the recovery room, with no irrigation.

Acute complications comprised significant hyponatraemia in two patients after standard TURP (serum sodium concentrations of 124 and 130 mmol/L) and one in the Gyrus group (serum sodium 113 mmol/L). These patients were successfully managed with frusemide, normal saline hydration and observation in the surgical intensive-care unit. Other short-term complications were limited to inability to void, requiring re-catheterization, in four after standard TURP and three (12%) after Gyrus TURP. The total acute complication rate was six of 18 (33%) in the standard TURP group and four (16%) of the Gyrus group. There were no major bleeding complications in either group.

For long-term complications, one patient in each group developed a bulbar urethral stricture which was treated successfully with internal urethrotomy. One patient in the Gyrus group later had external beam radiation therapy for the interval development of prostate cancer, and subsequently developed a bladder neck contracture. Last, one patient developed stress urinary incontinence after monopolar TURP, which was managed successfully with a periurethral bulking agent (Durasphere®). The present new TURP system appears to decrease the negative effects of surgery on the patient; the duration of catheterization was 44% shorter, hospital stay 43% less, acute complications 52% less common, and long-term complications 30% less common.

DISCUSSION

Despite new advances in MIT for LUTS related to BPH, TURP remains the standard surgical therapy [3]. Nonetheless, significant improvements in TURP technique have not often been reported. TURP remains associated with morbidity, the need for catheterization and for hospitalization with CBI. The present new TURP system appears to decrease the negative effects of surgery on the patient; the duration of catheterization was 44% shorter, hospital stay 43% less, acute complications 52% less common, and long-term complications 30% less common.

Other studies have already confirmed the utility of the Gyrus technique, yielding success rates comparable to conventional TURP. In a French study comprising 42 patients, the mean peak flow rate increased from 7.9 to 19.7 mL/s at 3 months of follow-up, and the IPSS decreased from 16 to 9 at 3 months after Gyrus TURP. There were no postoperative bleeding episodes, the mean catheterization time was 1.4 days, and the mean hospital stay 2.2 days [7]. In another study with 1 year of follow-up comparing standard and Gyrus TURP, both groups had no
statistically significant differences in postvoid residual urine, flow rates, symptom score, quality of life, length of stay and period of catheterization. Re-catheterization rates were higher in the Gyrus cohort (30% vs 9%), which was not so in the present series. Clot evacuation rates were higher in the monopolar TURP group (19% vs none), as might be expected in view of the haemostatic advantages of the Gyrus technique [6]. While these studies support the clinical efficacy of bipolar TURP, we endeavoured to determine if Gyrus TURP was also associated with less surgical ‘impact’ on the patient, i.e. shorter hospital stay and catheterization, and fewer complications. In the present series, while resected weights were similar, these three complications. In the present series, while resected weights were similar, these three measures were all better in the Gyrus cohort, although they only approached statistical significance (P = 0.1).

There were no major bleeding complications or episodes of clot retention requiring evacuation. While there were two cases of hyponatraemia in the monopolar TURP group, it was unexpected to find a case of hyponatraemia and pulmonary oedema in a patient who had TURP using the Gyrus system. The mechanism of this hyponatraemia cannot be fully explained by absorption of isotonic irrigation, and may be secondary to fluid shifts between the intravascular and extracellular compartments unrelated to the irrigant.

The present patients treated by Gyrus TURP had their catheter removed a mean of 1.4 days earlier than the standard group. The mean hospital stay was also almost a day (0.9) less. When the burden of catheterization and need for bladder irrigation is reduced, patient comfort, the hospital stay and costs also improve. Discharge 1 day earlier results in an anticipated saving of $1200 at our institution. Four patients with small prostates treated with the Gyrus system went home on the same day, effectively making their operation an outpatient procedure. This illustrates that in selected patients, CBI is not mandatory with the Gyrus system, further decreasing the effect of surgery on some patients.

In conclusion, these results for Gyrus TURP support previous reports that it is safe and effective. In this series the new system allowed us to discharge patients sooner and remove their catheters earlier, which benefits both patients and healthcare system, by reducing overall costs and the effects of surgery. There were fewer acute and long-term complications than with standard TURP. Because of these benefits and the tendency for less intraoperative bleeding associated with the Gyrus TURP, it has become the new standard of care at our institution. These data are promising, but a longer follow-up and larger series are needed before the Gyrus method becomes universally accepted for managing BPH.

CONFLICT OF INTEREST
Richard Santucci is a study investigator funded by sponsor. Source of funding: Gyrus Medical.

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Correspondence: Richard A. Santucci, Chief of Urology, Detroit Receiving Hospital, Wayne State University School of Medical, 4160 John R, Suite 1017, Detroit, MI 48201, USA. e-mail: rsantucc@med.wayne.edu

Abbreviations: MIT, minimally invasive therapy; CBI, continuous bladder irrigation.
Acute urinary retention: what is the impact on patients’ quality of life?

KAY THOMAS, GRENVILLE OADES, CATHY TAYLOR-HAY and ROGER S. KIRBY
Urology Department, St George’s Hospital, London, UK

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INTRODUCTION

Acute urinary retention (AUR) is a common urological emergency characterized by a sudden inability to pass urine, and associated with lower abdominal pain [1,2]. The immediate management of this condition varies among different institutions, but usually involves inserting either a suprapubic or urethral catheter, followed by medical therapy, a subsequent trial without catheter, and either TURP or discharge home with an outpatient follow-up [3,4]. In recent years the natural history and incidence of AUR has been better understood, but the impact of an episode of AUR on the patient has not been directly assessed [5–10]. The reported prevalence rates of AUR vary from 0.004 person-years to 0.015 and 0.13, depending on the patient group studied [5–10]. In the Olmsted county study of the natural history of BPH, the risk of an episode of AUR was identified as 1.6% at 5 years for men aged 40–49 and 10% at 70–79 years [10]. This finding implies that with an ageing population, AUR is likely to become an increasingly prevalent problem.

LUTS can significantly compromise the daily life of affected men, because of the degree of bother, interference with daily activities, degree of worry, psychological general well-being and general health [11–15]. Men with marked LUTS are also more worried and embarrassed [16]. The impact of urinary symptoms on health-related quality of life (HRQoL) is most pronounced when assessed using disease-specific measures, but has also been shown using more general QoL measures [11,14,15]. Although disease-specific instruments have been validated for BPH, none are specific to AUR [13,17,18].

The aim of the present pilot study was to evaluate the impact of admission for AUR on patients’ HRQoL compared with the impact of admission for elective surgery for BPH and renal colic (RC).

PATIENTS AND METHODS

A longitudinal observational trial was designed to compare quantitatively the impact of admission for an episode of AUR with that of elective surgery for BPH and RC. Consecutive patients eligible for the trial were recruited and followed for the duration of the study. Demographic details were taken at the first consultation (within 72 h of admission) and consenting patients were given a self-completion questionnaire. Patients were then required to attend the hospital and complete the questionnaire again at 1, 2, 3 and 6 months. Those who failed to attend were sent a second appointment, and if they failed to attend this a questionnaire was posted to them. The study was conducted in one centre during a 2-year period. Ethical approval for the study was obtained from the ethics committee before recruitment.

Three categories of patient were recruited simultaneously: group 1, men aged >50 years presenting to the accident and emergency (A&E) department with AUR; group 2, men aged >50 years admitted for elective surgery for BPH; and group 3, men aged >40 years presenting to A&E with RC. A self-completed HRQoL questionnaire was administered at five visits (72 h from admission, and 1, 2, 3 and 6 months afterward) over a 6-month follow-up.

RESULTS

Group 1 reported mean pain scores on admission of 7.7, compared with 5.6 for group 2 and 8.3 for group 3. Patients in group 1 had the most investigations and recurrent attendance to A&E throughout the study, compared with almost none for the other two groups. There was a substantial economic burden for group 1; 15% had extra help at home at a mean cost of £403 for the duration of the study. For the other domains assessed (e.g. emotions, mental state, general health) groups 1 and 2 were similar.

CONCLUSIONS

An episode of AUR has a measurable impact on patients’ HRQoL, which often occurs in the community and therefore may not be appreciated by the urology team providing their care. Further work is therefore required to improve the ‘patient journey’ for those with AUR, and to prevent patients developing AUR in the future.

KEYWORDS

acute urinary retention, catheterization, quality of life, BPH
with no adverse effect on their care. Patients excluded from the study were those with a diagnosed prostate cancer, history of alcohol abuse, cognitive impairment or circumstances that would prevent them completing the study, e.g. moving away from the area.

After the initial recruitment a self-completion questionnaire was administered; this was a combination of elements from several existing HRQoL and health-economic questionnaires (Table 1) [19–23]. Before use in this study it was piloted in a small sub-population of patients. The purpose of the questionnaire was to assess the impact of the conditions evaluated (AUR, BPH, RC) on various aspects of the patients HRQoL (Table 1) [19–23]. General demographic data, e.g. patient age, level of education, employment and marital status, were also collected. Details of drug and medical history were recorded at the first consultation only.

As patients were given no intervention as part of the study, only a descriptive analysis is given of the longitudinal trends and any similarity or dissimilarity between the groups. ANOVA was used to compare individual domain scores between the groups and with baseline.

## RESULTS

In all, 95 patients were recruited during the 2-year period, 43 in group 1, 35 in group 2 and 17 in group 3 (Table 2). Two-thirds (64) of the patients completed the entire study; 31 patients withdrew, including 19 lost to follow-up, eight who felt too ill to continue, two diagnosed with cancer, one who died and one with excessive work commitments.

The mean age of the whole group was 69.9 years, although group 3 was significantly younger (58.9 years) (Table 2). Groups 1 and 2 had a similar age, marital status, level of education and employment. In contrast, patients in group 3 tended to be younger and single, with a higher level of education and employment. Patients in groups 1 and 2 had higher levels of comorbidity, in particular hypertension, cardiac and gastrointestinal disease; >90% of these patients had at least one comorbid condition, compared with <70% of those in group 3.

Specific information about group 1 showed that it was the first episode of AUR for two-thirds of them; the episode of AUR was spontaneous in most (63%). The most common precipitants were a surgical procedure (11%), UTI (6%) and new medication such as an anticholinergic agent (5%).

Twice as many patients in group 2 (35%) reported being hospitalized overnight or longer during the 3 months before admission for surgery than those in group 1 (21%) at visit 1 (Table 2), but mean hospitalization for group 1 was longer, at 11.2 vs 7.2 days, for group 2. Only 12% of group 3 were hospitalized during this period, for a mean of 5 days. Over the duration of the study, 20% of group 1 reported admission to hospital at each visit, compared with a gradual reduction to almost zero in the other two groups (Table 2).

The rates of consulting a doctor during the 3 months before the study were comparable among the groups, except for attendance at A&E by those in group 2, which was almost...
twice that of group 1. Groups 2 and 3 reported no attendance at A&E by visit 3, compared with group 1, with patients reporting a mean of one attendance between each visit (Table 2).

Group 2 had almost twice as many specialized investigations during the 3-month period before admission (44%) than group 1 (29%) and 2 (25%), but over the course of the study group 1 consistently had more tests than the other two groups.

None of the patients reported long absences from work because of their urinary problem, with all three groups reporting missing only 1–2 days. However, there was an economic effect on group 1 in particular, with up to 15% of patients reporting that they had needed to pay someone to help them around the house with housework and preparing meals (Table 2). On admission, none in group 3 required help and only 6% of group 2 did so. Group 1 also required help from relatives and friends for longer (visits 1–3) than group 2 (visits 1–2), with group 3 needing no help. The average amount paid for the extra work required to support the patients at home during the course of the study was £403, £82 and nothing in groups 1–3, respectively.

Group 2 reported the lowest mean levels of pain from their condition, with 39% having had none in the 24 h before admission, compared with 7% in group 1 and 6% in group 3. The mean worst pain, assessed by a visual analogue score from 0 (no pain) to 10 (extreme) was highest in group 3 (8.3) but still higher in group 1 (7.7) than in group 2 (5.6). However, patients in group 1 reported the greatest relief of pain after a procedure (catheterization); they had a mean relief score of 7.7, which was significantly greater (P < 0.01) than the relief for both group 3 (5.9) and 2 (4.3).

For six of the seven domains evaluated, the interference of pain with activities was greatest for patients in group 1 at the screening visit, with group 2 reporting the lowest level of interference. Patients in all three groups had a dramatic decrease in the level of interference after 1 month, with all reporting the greatest interference from pain on sleep and enjoyment of life (Fig. 1a).

The results for all seven prostate symptoms of the IPSS were similar for patients groups 1 and 2. The means halved from visit 1 to visit 2, and remained approximately constant throughout the next 3 months. On average patients in all groups improved from being ‘mostly dissatisfied’ with their ‘feelings about spending the rest of their life with your urinary condition’ at visit 1 to being ‘mostly satisfied’ by visit 5 (Fig. 1b).

The BPH Impact Index contains four questions about discomfort, worry, bother and limitation of activities caused by urinary problems during the past month. Patients in groups 1 and 2 reported similar levels of improvement from ‘some’ to ‘a little’ in terms of the impact of their urinary problems on discomfort, worry and bother. Similar trends towards improvement were reported for the limitation of activities. Patients group 3 reported no significant changes in any of the areas measured over the five study visits (Fig. 1c).

The BPH Symptom Interference Assessment evaluated interference in seven activities caused by urinary problems. As with the BPH Impact Index, patients in groups 1 and 2 reported similar levels of improvement from ‘some of the time’ to ‘a little of the time’ for interference of their urinary problems on the
seven activities. In general, patients in group 2 reported slightly more time with symptom interference than those in group 1. Except for ‘playing outdoor sport’ and ‘going out’, group 3 had no significant changes in their interference scores over the five visits. For these two domains group 3 reported an increase in interference at visits 2 and 3, which settled to levels equal to those before admission by visits 4 and 5.

The ‘Urinary-specific Worries and Concerns’ questions evaluated worry and embarrassment about urinary function, worry about prostate cancer and concern about sexual function. Groups 1 and 2 reported similar trends to being less worried or concerned over the five visits, whilst negligible change was reported in worries or concerns by group 3.

The Hospital Anxiety and Depression Scale showed that the present were not depressed. In general, patients in groups 1 and 2 were very similar and in group 3 they reported slightly more negative feelings. By visit 5, patients in group 3 differed significantly from group 1 for all questions except losing interest in appearance and getting sudden feelings of panic.

Using the Euro-Qol instrument, the present patients reported no problems with mobility, self-care or anxiety/depression. There were general trends toward improvements in ‘performing usual activities’ and small improvements in ‘pain/discomfort’, although there were no statistically significant differences among the groups.

The ‘Health State Today’ showed a trend towards a general improvement in overall health amongst patients in all three groups over the course of the study, but with no statistically significant differences.

The Short Form-12 showed that patients in group 3 reported feeling significantly more ‘downhearted and blue’ than patients in groups 1 and 2. There were virtually no differences among the three groups for ‘health in general’ or the other physical and emotional domains that are part of this instrument.

The specific urinary symptom questions were completed only by groups 1 and 2. When asked how worried or concerned they were about not being able to urinate, group 1 were very concerned, scoring 7.7 (0, not worried; 10 extremely worried) at admission, compared with group 2, scoring 5.7. However, there was a progressive trend towards being ‘not at all worried or concerned’ for both groups 1 and 2 during the study. Similar levels were reported by both groups of patients when asked how worried or concerned they were about the treatment or procedure being successful for their urinary symptoms.

**DISCUSSION**

In the present study, AUR had an impact on some aspects of patients’ HRQoL; in particular, they had high pain scores (7.7) on admission, which resolved over the duration of the study. There was also a substantial economic burden on patients after an episode of AUR, with a significant percentage (15%) having to pay for extra assistance at a mean cost of £403 over the course of the study. Another adverse impact was the many attendances to A&E or admission to hospital (20%) reported by group 1 throughout the study, and the additional investigations that they required.

This was a pilot single-centre study; some of the changes recorded may be related to the process of managing an episode of AUR in our institution. Also, because the initial aim of the study was to assess the HRQoL, limited urological data were obtained from the questionnaires. This could have been relevant to some of the observations. However, there were some clear differences among the groups, which could form the basis for a wider study recruiting more patients across several sites.

In summary, AUR seems to have a measurable impact on patients’ HRQoL, and which persists well beyond the initial presentation. Much of this effect occurs when patients have been discharged home and therefore may not be appreciated by the urology team providing their care. With increasing pressures on hospital services in the UK, most patients are now discharged home with a urethral catheter after an episode of AUR, to await further management [24]. These data provide a rationale for preventive measures in patients at risk of developing AUR, by the judicious use of pharmacotherapy with either a 5α-reductase inhibitor or a combination of a 5α-reductase inhibitor and an α-blocker [25–27]. Further work is required to evaluate other strategies which could be used to improve the ‘patient journey’ for those with AUR.

**ACKNOWLEDGEMENTS**

Merck Sharp and Dohme were involved in the funding and data analysis of the study.

**CONFLICT OF INTEREST**

Cathy Taylor-Hay is a study investigator funded by sponsor. Roger Kirby has given talks at MSD, Pfizer and Abbot Symposia.

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Correspondence: Kay Thomas, Urology Specialist Registrar, Urology Department, Guy’s Hospital, London, UK. e-mail: specialkthomas@hotmail.com

Abbreviations: AUR, acute urinary retention; HRQoL, health-related quality of life; RC, renal colic; A&E, accident and emergency.
Systemic stress responses in patients undergoing surgery for benign prostatic hyperplasia

BORIS RUZIC, IGOR TOMASKOVIC, DAVOR TRNSKI, OGNJEN KRAUS, MIROSLAV BEKAVAC-BESLIN* and NADA VRKIC†
Departments of Urology, and †Clinical Institute of Chemistry, School of Medicine, University of Zagreb, and *Department of Surgery, University Hospital Sisters of Mercy, Zagreb, Croatia

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OBJECTIVE
To determine differences in systemic stress responses in patients undergoing three different types of surgery for benign prostatic hyperplasia (BPH), evaluated by measuring levels of stress variables, i.e. cortisol; acute-phase reactants, i.e. C-reactive protein (CRP) and fibrinogen; and antioxidants, i.e. total antioxidant status (TAS) and superoxide dismutase (SOD).

PATIENTS AND METHODS
The study included 80 patients who fulfilled the inclusion criteria for surgery for BPH. Based on an ultrasonographic estimate of the prostate volume before surgery, all patients were allocated to one of three groups; group 1, prostate ≤30 g and treated with transurethral incision of the prostate (TUIP); group 2, prostate 30–80 g, treated with transurethral resection of the prostate (TURP); and group 3, prostate >80 g, treated with a suprapubic transvesical prostatectomy (TP). Blood samples were taken from each patient on the day before and the day after surgery, and the acute-phase reactants and antioxidants measured; cortisol concentrations were also measured in 24-h urine samples the day before and 3 days after surgery.

RESULTS
There were significantly higher levels of cortisol, CRP and TAS, and significantly lower levels of fibrinogen and SOD in all study groups after surgery than before. Surgery and associated conditions, e.g. excitement, fear, blood loss, etc., lead to traumatic and oxidative stress, followed by a strong systemic stress response during and after surgery. Low fibrinogen levels after surgery had a different pattern from the other acute-phase reactants, as a result of increased fibrinolytic activity after TURP and TP.

CONCLUSION
The extent of the systemic stress response correlated fairly well with the degree of tissue damage, which differed in the three groups. Suprapubic TP caused the most tissue trauma and triggered the strongest systemic stress response. This response was moderate after TURP, while TUIP (a minor intervention) caused the least stress. Specific changes in stress markers could be used to improve surgery for BPH. Whether there is a benefit of antioxidant therapy during surgery for BPH should be evaluated in further studies.

KEYWORDS
acute phase reactant, antioxidants, cortisol, oxidative stress, stress parameters, surgery of BPH

INTRODUCTION
People are constantly exposed to numerous physical, psychological, chemical and social factors that jeopardize their physiological equilibrium. Every condition that threatens the state of homeostasis is considered a stress, and causes leading to it are termed stress factors. They have their effect through humoral and neural pathways, which together lead to many organ reactions. Stress response is the term used for the hormonal and metabolic changes which follow injury or trauma. After early work on the stress response to accidental injury, attention turned to surgical trauma, and responses to most types of surgery were reported [1]. A systemic stress response is the general reactivity of an organism and is unpredictable at the individual level. All components of the systemic stress response aim to protect the organism and avoid danger.

Objective signs of stress include, among many others, high serum levels of adrenocorticotropic hormone, adrenaline and cortisol, depletion of serum eosinophils, elevation of insulin, somatotropin in blood, increase in arterial blood pressure, and changes in electrical activity of the brain.

Subjective signs of stress include excitement, palpitations, impulsive behaviour, fear, etc.

A sensitive method for stress evaluation implies measuring stress factors which are important in the acute-phase reaction, i.e. cortisol, catecholamines, acute phase proteins and antioxidants, in states of oxidative stress. Serum levels of these vary in infection, infarction, surgery, burns and malignant diseases.

Cortisol is a glucocorticoid, secreted from cortex of suprarenal gland; its role in gluconeogenesis, metabolism of fat, CNS, muscle and renal function, vascular reactivity and the immune response has been studied extensively and is well known. It is also considered to be a surgical stress indicator [2]. The serum level increases in operated patients and directly correlates with the extent of surgical trauma [1]. Measuring serum cortisol during surgery indicates the extent of immediate stress, while its concentration in 24-h urine samples shows overall stress on that day.

Acute-phase reactants are a heterogeneous group of proteins that mediate the acute-phase response [3]. Their function is to induce a nonspecific host defence and limit the local immune response. In the present study we analysed C-reactive protein (CRP) and fibrinogen.

Antioxidants are compounds that prevent oxidative reactions; their presence is of
great benefit in infections as they are thought to be underlie the cellular immune response. Disequilibrium between free radical production and scavenging leads to a state of oxidative stress [4], which represents excessive production of oxygen-free radicals that can harm cell structure and function, changing DNA, proteins, carbohydrates and fats. These oxidative chain reactions could cause oxygen depletion, as every O_2 molecule is a source of new free radicals and such reaction results in cell damage. Moreover, reactive oxygen species, e.g. hydrogen peroxide, enhance oxidative stress. Some studies have suggested that they are tumour promoters [5]. Antioxidants have a protective role and are classified in three groups, i.e. antioxidative enzymes, antioxidative scavengers and preventive antioxidants. In the present study we measured total antioxidant status (TAS) and superoxide dismutase (SOD). TAS corresponds to the total antioxidant reserve of the organism, and SOD is the most active antioxidative enzyme, catalysing the decomposition of superoxide radical into hydrogen peroxide. The level of SOD in serum is high in cases of mitochondrial degradation and cell death.

Surgical stress has aroused much interest recently; most studies investigated the degree of surgical stress by comparing laparoscopic and classical surgical procedures [6–9], and most included cortisol, CRP, some haptoglobin, and some cytokines (interleukin-2 and -6) to assess the systemic response to surgery. Studies to assess stress in urological procedures are scarce [10], and to the best of our knowledge there are none investigating surgery for BPH.

Thus we report a prospective, controlled, unrandomized study to determine the degree of systemic stress response to endoscopic and open surgical procedures for BPH, evaluated by measuring levels of stress variables, i.e. cortisol, acute-phase reactants (CRP and fibrinogen) and antioxidants (TAS and SOD).

PATIENTS AND METHODS

Eighty men (mean age 72 years, range 50–88) scheduled for surgery for BPH in the authors’ institution were consecutively included in the study after obtaining informed consent. The study was approved by the regional ethical committee. According to the estimated mass of the prostate by TRUS [3, 5 and 7 Hz, Sonoline SI-400, Siemens, Germany] patients were allocated to three groups: group 1 (30 men), prostate ≥30 g, treated by transurethral incision of the prostate (TUIP); group 2 (40 men), prostate 30–80 g, treated by TURP; and group 3 (10 men), prostate ≥80 g and who had a suprapubic transvesical prostatectomy (TP).

The statistical analysis accounted for differences in the size of the groups, reflecting the frequency of each procedure; appropriate statistical tests were used accordingly. Inclusion criteria were no suspicion of cancer on a DRE, a PSA level of ≤4 ng/mL, an IPSS of ≥20, a maximum urinary flow rate on uroflowmetry of ≤15 mL/s, and residual urine of ≥200 mL. Exclusion criteria were haematuria, UTI, urethral stricture, previous prostate surgery, a suspicion of prostate cancer (DRE, PSA or TRUS), neurological, psychiatric and malignant disease, impairment of liver or renal function, and intake of anti-inflammatory or immunosuppressive drugs. The initial values of PSA, IPSS and maximum flow rate were not significantly different among the groups. All patients had surgery under spinal anaesthesia.

Cortisol was determined from 24-h urine samples, while CRP, fibrinogen, SOD and TAS were determined from sera. A blood sample was taken on the day before and 1 day after surgery, and the serum level of acute-phase reactants (CRP and fibrinogen) and antioxidants (SOD and TAS) measured. Urine samples were collected 24 h on the day before and again 3 days after surgery to determine cortisol levels.

The CORT-CT2 radioimmunoassay kit (CISbiointernational, Schering SA, France) was used to measure cortisol in urine and the 24-h excretion calculated by multiplying the urine cortisol concentration by the urine volume over 24 h. CRP was determined in sera using the Immuno-Turbidimetric test (Olympus System Reagent, turbidimetric fixed-time method; Olympus Diagnostica GmbH, Ireland). Fibrinogen was measured using a nephelometer assay (Turbox®, Orion Diagnostica, Finland) and the Turbox/Turbox plus analyser. TAS was determined by spectrophotometry using a TAS kit (Random Lab. Ltd., Crumlin, Great Britain), and SOD similarly using the RanSOD kit (Random).

Results are expressed as the mean (±) and range; to compare paired values within the same group the nonparametric Wilcoxon test, and to compare data among the groups the nonparametric Kruskal–Wallis test, was used. To compare the groups the Wilcoxon test of range of means and the Mann–Whitney U-test was used; in all tests P<0.05 was considered to indicate statistical significance.

RESULTS

All the patients were relieved of their obstructive symptoms at 1, 3, 6 and 12 months of follow-up. The follow-up included the IPSS questionnaire, uroflow and residual urine measured by TRUS; none of the patients were incontinent.

The hospitalization after TUIP, TURP and TP was 3 (2–5), 6 (4–9) and 10 (8–14) days. None of the men required re-operation and there was no need for additional treatment during first year of follow-up. One patient had epididymitis on the fourth day after TP; he was treated conservatively. Two patients had macrohaematuria 3 weeks after TURP, from the prostatic fossa; they were also treated conservatively. The values of all the variables assayed, and the significant differences before and after surgery, are shown in Table 1.

DISCUSSION

BPH is one of the most common problems encountered in urology and clinical medicine; there are several approaches to treating it, both by drugs and surgery. Thus we compared TUIP, TURP and TP for the surgical stress caused by each. Cortisol was high before surgery in all three groups of patients; we suggest that hospitalization, fear of surgery and anxiety contributed to this result, regardless of the type of surgery. The increase after surgery was substantial, as all treatments caused surgical stress. Even 3 days after surgery patients had high urinary cortisol levels, suggesting that there was still excessive production and that the body was stressed. As cortisol correlates with the extent of surgical trauma it is clear that TP caused the greatest and TUIP the least stress. TURP caused greater but not significantly more stress than TUIP, possibly because both operations are transurethral, leaving the body cavities intact and directly resecting only the prostate, while in TP the skin, subcutaneous...
tissue and muscle fasciae are resected before reaching the prostate. Cortisol could be changed under different types of anaesthesia, but as all patients had spinal anaesthesia that cannot account for the difference. Other causes of change in cortisol other than surgery could be fear, smoking, hypovolaemia (bleeding), thyroid, hepatic and renal function. Some investigators corrected urinary cortisol (bleeding), thyroid, hepatic and renal function.

Cortisol could be measured by laboratory tests such as CRP.

Increased fibrinogen, as an acute-phase protein, can be used to estimate inflammation; minimally invasive surgery causes higher levels, but surgery accompanied by significant blood loss decreases the level. Bleeding increases the use of fibrinogen and thus reduces the levels after prostate surgery.

The level of oxidative stress can be measured by estimating free radicals or antioxidants; more recently, TAS has been used as a measure of antioxidant reserve [15]. Antioxidants have been studied mostly in cardiovascular and malignant diseases. Van Driel et al. [16] found SOD activity to be less in colon cancer, especially in adenocarcinomas, and Sun [17] reported similar findings. Laparoscopic causes less stress than open surgery [18,19]. Oxidative stress in urology has been assessed in kidney transplantation and in ESWL [20,21], but oxidative stress and BPH have not been evaluated, to our knowledge. The mean TAS levels before surgery were within the normal range in all groups, with no differences. After surgery, patients in all three groups were in a state of oxidative stress; group 3 had higher values than groups 1 and 2, and group 2 higher levels than group 1. As noted, this is another objective variable of stress and the results agree with the dynamics of the other stress variables. SOD was determined in erythrocytes; it is very active especially when flooded with free radicals, e.g. during ischaemia and reperfusion. The level of SOD is lower on the first day after surgery and decreases if a procedure causes more severe oxidative stress. The lowest levels of SOD were measured after TP. There is no firm view of the level of SOD in different conditions; the present men were mostly elderly, and with concomitant respiratory, cardiac, rheumatic and other diseases that could alter the results. The decrease in SOD level after surgery could also be explained by the reduction in BPH tissue, which could be responsible for an excessive production in free radicals before surgery and consequently increased SOD.

### Table 1: The values of the stress variables assessed before and after surgery in each group.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1, TURP</th>
<th>Group 2, TURP</th>
<th>Group 3, TP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>before</td>
<td>after</td>
<td>before</td>
</tr>
<tr>
<td>Cortisol, nmol/L</td>
<td>419.3 (247.6)</td>
<td>491 (521.4)</td>
<td>424.1 (191.6)</td>
</tr>
<tr>
<td>CRP, mg/mL</td>
<td>[122–992]</td>
<td>[210–912]</td>
<td>[102–980]</td>
</tr>
<tr>
<td>Fibrinogen, g/L</td>
<td>5.76 (10.2)</td>
<td>28.4 (14.5)</td>
<td>9.78 (19.1)</td>
</tr>
<tr>
<td>g/L</td>
<td>[0.1–4.6]</td>
<td>[2.5–66.4]</td>
<td>[0.0–96.2]</td>
</tr>
<tr>
<td>TAS, mol/L</td>
<td>5.4 (1.8)</td>
<td>5.1 (1.6)</td>
<td>5.8 (1.8)</td>
</tr>
<tr>
<td>CRP</td>
<td>[3.4–12.0]</td>
<td>[2.6–10.1]</td>
<td>[3.0–11.0]</td>
</tr>
<tr>
<td>Fibrinogen, mol/L</td>
<td>[1.42–1.86]</td>
<td>[1.39–1.96]</td>
<td>[1.32–1.82]</td>
</tr>
<tr>
<td>SOD, U/mL</td>
<td>177 (64.7)</td>
<td>146.6 (46.1)</td>
<td>173.8 (59.4)</td>
</tr>
<tr>
<td>U/mL</td>
<td>[72–305]</td>
<td>[56–235]</td>
<td>[31–294]</td>
</tr>
</tbody>
</table>

Reference ranges: cortisol 72.5–372 nmol/L; CRP 0–5 mg/L; fibrinogen 3.0–6.0 g/L; TAS 1.30–1.77 mmol/L; SOD 164–240 U/mL.

P values – cortisol: before, no significant differences among groups, but 1 and 2 were above reference range. Before vs after: 0.011, 0.041 and 0.007, groups 1, 2 and 3, respectively; after, group 3 vs 1 and 2. CRP: no difference before but all above the normal range; before vs after <0.001, <0.001 and 0.005 groups 1, 2 and 3, respectively; after, group 3 vs 1, <0.001 and vs 2, 0.043, no difference 1 vs 2. Fibrinogen: no significant difference before; before vs after, group 2, <0.001 and 3, 0.028 after among groups, 0.008, and 2 and 3 vs 1 0.003 and 0.048, respectively, no difference 2 vs 3. TAS: no difference before; before vs after 0.032, <0.001 and 0.014, 1, 2 and 3, respectively but still within referral range; after, 3 vs 2 0.043, and 1, 0.028, 2 vs 1 0.032. SOD before not significantly different; after 3 vs 2, 0.025 and 3 vs 1, <0.001; no difference 2 vs 1.
antioxidant level could also be affected by anaesthesia (but not in the present study), antibiotics and analgesics.

The extent of the systemic stress response correlated fairly well with the degree of tissue damage, which differed in the three groups. Supra pubic TP caused the most tissue trauma and triggered the strongest systemic stress response; the stress response was moderate after TURP, while TUPIP, as a minor intervention, caused the least response.

Specific changes in stress markers could be used to improve surgery for BPH. Whether there is any benefit from preventive or perioperative antioxidant therapy [22] during surgery for BPH should be evaluated in further studies.

CONFLICT OF INTEREST

None declared. Source of funding: departmental budget.

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Correspondence: Boris Ruzic, Department of Urology, University Hospital Sisters of Mercy, Vinogradarska cesta 29, 10000 Zagreb, Croatia. e-mail: boris.ruzic@zg.htnet.hr

Abbreviations: CRP, C-reactive protein; TAS, total antioxidant status; SOD, superoxide dismutase; TUPIP, transurethral incision of the prostate; TP, transvesical prostatectomy.
Improved quality of life in patients with overactive bladder symptoms treated with solifenacin

CON J. KELLEHER, LINDA CARDOZO*, CHRISTOPHER R. CHAPPLE†, FRANCOIS HAAB‡ and ARWIN M. RIDDER¶

Guy's and St. Thomas' Hospital, *King's College Hospital, London, †Royal Hallamshire Hospital, Sheffield, UK, ‡Hôpital Tenon, Paris, France and ¶Yamanouchi Europe BV, Leiderdorp, the Netherlands

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OBJECTIVE
To assess the effect of solifenacin succinate treatment on quality of life (QoL) measured in clinical trials in patients with overactive bladder (OAB).

PATIENTS AND METHODS
QoL data using the King’s Health Questionnaire (KHQ) were analysed from two phase-3, 12-week studies (1984 patients) and a long-term extension of these studies (1637 patients) where patients received solifenacin for up to an additional 40 weeks (i.e. a 52-week exposure to solifenacin). The 12-week studies were multinational, multicentre, randomized, double-blind, and placebo-controlled. The 10 domains from the KHQ evaluated were general health perception, incontinence impact, role limitations, physical limitations, social limitations, personal relationships, emotions, sleep/energy, severity measures, and symptom severity. Changes from baseline to endpoint in QoL variables were assessed by analysis of variance, and from pooled outcomes of the 12-week studies by analysis of covariance. Descriptive statistics were used to evaluate data in the extension study.

RESULTS
In the two 12-week studies (1033 and 857 patients), those receiving once-daily solifenacin had statistically significantly better QoL than those on placebo. Changes in the KHQ were statistically significantly (P < 0.05) different from placebo for both solifenacin 5 and 10 mg once daily on five of the 10 KHQ domains in each of the studies. Pooled data from the two 12-week studies showed statistically significant (P < 0.05) differences from placebo for both solifenacin doses in nine of the 10 domains. Improvements in QoL scores for solifenacin were 35–48% in nine of the 10 domains for the 1347 patients providing QoL data in the extension study. About two-thirds of this overall improvement occurred during the original 12-week study, with an additional third reported during the extension, with an improvement in QoL over time in patients treated with solifenacin.

CONCLUSIONS
Results from the KHQ in study participants in the two double-blind studies showed that solifenacin significantly improved the QoL in patients with OAB symptoms after 12 weeks of treatment, with further improvements during long-term administration up to 1 year. Clinical trial outcomes show a favourable balance of efficacy and tolerability with solifenacin; the present report further supports this efficacy and tolerability by providing evidence for both short- and long-term improvements in QoL.

KEYWORDS
antimuscarinic, overactive bladder, quality of life, solifenacin succinate

INTRODUCTION
About 50–100 million people worldwide are estimated to be affected by symptoms of the overactive bladder (OAB) syndrome. It is more common than diabetes mellitus or peptic ulcer, and of similar prevalence to asthma or chronic bronchitis [1,2]. The OAB is known to adversely affect the quality of life (QoL) of sufferers, and perhaps the greatest benefits of treatment experienced by patients are improvements in QoL.

Two recent surveys, one from Europe comprising nearly 17 000 men and women, and the other from the USA comprising 5000 men and women, estimated similar overall prevalence rates of 16.6% and 16.5%, respectively [3,4]. The European survey was the first to report prevalence rates for a large population using a symptom-based definition of OAB. That analysis focused on urgency, urge incontinence and frequency as the primary symptoms of OAB, and was designed to exclude patients with possibly confounding conditions such as UTIs, pure stress incontinence or prostatic obstruction. Survey items were phrased to capture symptoms that were chronic or bothersome, and most participants reported having symptoms for >1 year [3]. In addition, 65% of respondents reported that their symptoms of OAB adversely affected their daily lives [3].

In the USA survey, the symptoms of OAB were associated with high depression scores and poor quality of sleep [4]. Sleep disturbances in patients with OAB may result in daytime somnolence, interference with cognitive function, impaired concentration, and diminished physical and mental health [5]. The incidence of anxiety and low self-esteem also appeared to be relatively high among people with OAB [6]. Untreated OAB is associated with an increased risk of UTIs, skin infections and injury in a fall, that for the elderly is a common cause of both morbidity and mortality [7,8].

Solifenacin succinate is a once-daily oral antimuscarinic agent evaluated for treating OAB, with a suggested starting dose of 5 mg once daily. The efficacy, safety and tolerability of solifenacin were reported in four pivotal phase-3 studies conducted globally, and in a large, open-label, long-term extension study.
Solifenacin 5 and 10 mg once daily were both shown to produce statistically significantly less urgency, urge incontinence and frequency than was placebo [9]. In one phase-3 clinical trial, 51% of patients reporting urinary incontinence at baseline were continent with either solifenacin 5 or 10 mg once daily by the end of the 12-week study [10]. There were also statistically significant increases in volume voided per void with solifenacin 5 and 10 mg once-daily [8]. In an open-label extension study of solifenacin, the continence rate, reported as 51% after 12 weeks of treatment, rose to 60% by the end of the study.

Solifenacin was also well tolerated in these trials; 11% of patients receiving solifenacin 5 mg once daily reported dry mouth, compared with 28% of patients receiving 10 mg once daily and 4% receiving placebo. Solifenacin had no effect on vital signs, hepatic function or clinical laboratory variables, and no increased risk of serious adverse effects were associated with its use.

The ICS recommended that QoL measures be included in all studies evaluating treatments for OAB as a complement to measures of urinary symptoms. QoL questionnaires quantify the bother caused by OAB symptoms, the associated QoL impairments, and the improvements in both after successful treatment [11]. They also provide an insight into the clinical relevance of efficacy measures and their relation to patient satisfaction, and are the only means of assessing the overall impact of OAB on a patient’s life [12].

Several instruments have been developed to measure QoL. Generic questionnaires designed to assess large populations with many different conditions cover a broad spectrum of items, but fail to address the specific impact of OAB symptoms and are relatively insensitive outcome measures for changes in bladder symptoms. Disease-specific OAB QoL questionnaires are designed to address the impact of urinary symptoms on patients’ QoL and are more effective in identifying issues relevant to patients with OAB, and to their clinicians [6,13]. The King’s Health Questionnaire (KHQ), used to measure QoL in the present report, is considered an effective disease-specific instrument and has been granted a Grade A recommendation by the WHO [14].

There are few published data on evaluating the impact of other OAB treatments on QoL. A study of long-term extended-release oxybutynin use assessed QoL using an incontinence impact questionnaire, a sleep impact questionnaire, and general health and bother (urinary leakage and/or bladder problem) scales [15]. For all these tools there were statistically significant improvements over baseline values at 1 year [15]. A study on extended-release tolterodine evaluated QoL using the KHQ [16,17]; the statistically significant improvements in QoL were sustained over 12–15 months [18].

In the present report we present QoL data from clinical trials evaluating solifenacin as a treatment for patients with OAB. Patient QoL data were obtained using the KHQ in two 12-week studies and a long-term extension of these studies, in which QoL served as a secondary efficacy variable.

### PATIENTS AND METHODS

Data on QoL variables were analysed from two 12-week multinational, multicentre, double-blind randomized studies [9,19], and an open-label extension of these studies, all involving adult men and women with symptomatic OAB. In the 12-week studies, placebo or solifenacin 5 or 10 mg were administered once daily. The study by Chapple et al. [9] treated 1077 patients and that by Cardozo et al. [19] 907 patients. The 40-week extension study was open-label and enrolled 1637 patients from the two 12-week studies.

The KHQ is a short, sensitive, condition-specific instrument that uses patient-reported outcomes to measure the treatment effects on health-related QoL. It contains 21 questions distributed among nine domains, plus a 10th domain containing 11 questions designed to identify individual bladder problems and their effects on the patient (Table 1) [16]. Because the KHQ has several validated language translations it is ideal for multinational clinical trials [12].

The KHQ offers a rapid appraisal in various clinical settings and contains questions about the bother and effects of specific bladder symptoms on QoL [16]. In a multinational clinical trial conducted over 12 weeks and involving 1284 patients, psychometric testing supported the reliability and validity of the questionnaire as an OAB-specific measure of health-related QoL [17].

Patients in the two 12-week studies evaluated in this report were supplied with the questionnaire at visit 2 (the start of double-blind treatment), visit 3 (after 4 weeks of double-blind treatment), and visit 5A (at the end-of-study visit after 12 weeks of treatment). At visit 2, patients were instructed on the completion of the questionnaire. To avoid potential bias, patients completed the questionnaire in the absence of the investigating staff. If required, e.g. with

### TABLE 1 The 10 domains of the KHQ [16], and the changes in the domain scores from baseline to study end in the two 12-week placebo comparator studies (1033 and 857 patients)

<table>
<thead>
<tr>
<th>QoL domain</th>
<th>N questions</th>
<th>Study 1 Placebo 5 mg</th>
<th>Study 2 Placebo 5 mg</th>
<th>Study 1 Placebo 10 mg</th>
<th>Study 2 Placebo 10 mg</th>
<th>Study 1 Solifenacin 5 mg</th>
<th>Study 2 Solifenacin 5 mg</th>
<th>Study 1 Solifenacin 10 mg</th>
<th>Study 2 Solifenacin 10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>General health perception</td>
<td>1</td>
<td>-1.7</td>
<td>-4.3</td>
<td>-3.5</td>
<td>-2.3</td>
<td>-5.8</td>
<td>-4.5</td>
<td>-3.0</td>
<td>-3.0</td>
</tr>
<tr>
<td>Incontinence impact</td>
<td>1</td>
<td>-17.8</td>
<td>-22.4</td>
<td>-23.6</td>
<td>-20.1</td>
<td>-27.0†</td>
<td>-30.3†</td>
<td>-24.4</td>
<td>-24.4</td>
</tr>
<tr>
<td>Role limitations</td>
<td>2</td>
<td>-14.7</td>
<td>-20.6*</td>
<td>-21.5</td>
<td>-15.9</td>
<td>-21.9†</td>
<td>-24.4†</td>
<td>-24.4</td>
<td>-24.4</td>
</tr>
<tr>
<td>Physical limitations</td>
<td>2</td>
<td>-11.9</td>
<td>-18.2*</td>
<td>-17.8</td>
<td>-15.4</td>
<td>-19.2</td>
<td>-22.3†</td>
<td>-22.3</td>
<td>-22.3</td>
</tr>
<tr>
<td>Social limitations</td>
<td>2</td>
<td>-7.0</td>
<td>-11.9</td>
<td>-10.9</td>
<td>-9.0</td>
<td>-12.1</td>
<td>-11.7</td>
<td>-11.7</td>
<td>-11.7</td>
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<tr>
<td>Personal relationships</td>
<td>3</td>
<td>-9.7</td>
<td>-9.2</td>
<td>-10.0</td>
<td>-9.4</td>
<td>-8.5</td>
<td>-8.3</td>
<td>-8.3</td>
<td>-8.3</td>
</tr>
<tr>
<td>Emotions</td>
<td>3</td>
<td>-12.5</td>
<td>-17.2*</td>
<td>-17.3*</td>
<td>-12.2</td>
<td>-16.4*</td>
<td>-16.6*</td>
<td>-16.6</td>
<td>-16.6</td>
</tr>
<tr>
<td>Sleep/energy</td>
<td>2</td>
<td>-9.3</td>
<td>-12.8</td>
<td>-12.7</td>
<td>-11.4</td>
<td>-15.4*</td>
<td>-15.9*</td>
<td>-15.9</td>
<td>-15.9</td>
</tr>
<tr>
<td>Severity measures</td>
<td>5</td>
<td>-6.9</td>
<td>-12.4†</td>
<td>-13.2†</td>
<td>-7.2</td>
<td>-9.6</td>
<td>-11.8†</td>
<td>-11.8</td>
<td>-11.8</td>
</tr>
<tr>
<td>Symptom severity</td>
<td>11</td>
<td>-2.2</td>
<td>-3.3†</td>
<td>-3.2†</td>
<td>-2.4</td>
<td>-3.4†</td>
<td>-3.4†</td>
<td>-3.4</td>
<td>-3.4</td>
</tr>
</tbody>
</table>

P < 0.05, f < 0.01, f < 0.001; As a hierarchical test was used for the solifenacin doses, P values are not shown for all domains for solifenacin 5 mg vs placebo; only P values indicating statistical significance are shown.
A higher domain score corresponds to a greater impairment of QoL for that domain [13,16].

Changes from baseline to end of study in domain scores, derived from the answers to the individual questions, were analysed. In the two 12-week studies, changes from baseline were assessed by ANOVA, including treatment as a fixed factor. A hierarchical (step-down) test procedure was used, with comparison of solifenacin 10 mg once daily with placebo tested at the two-sided 0.05 significance level using the corresponding contrast. If there was a statistically significant difference the comparison of solifenacin 5 mg once daily with placebo was similarly tested. The extension study used descriptive statistics.

RESULTS

Results from the KHQ assessments indicated that patients receiving once-daily solifenacin had statistically significant improvements in many disease-specific aspects of QoL. In one of the 12-week studies, 1033 patients provided QoL data; the change from baseline to study end (with baseline included as a covariate) was statistically better than with placebo for both solifenacin 5 and 10 mg once daily for five of the 10 domains (role limitations, physical limitations, emotions, severity measures and symptom severity; Table 1). For the incontinence impact domain, solifenacin 10 mg once-daily was significantly better than placebo.

In the other 12-week study, 857 patients provided QoL data; the change from baseline to study end (with baseline included as a covariate) was statistically significantly different from baseline for the incontinence impact, role limitations, emotions, sleep/energy, and symptom severity domains for both solifenacin 5 and 10 mg once daily. Solifenacin 10 mg was also significantly different for the physical limitations and severity measures (Table 1).

Pooling of data from the two 12-week studies showed statistically significant differences against placebo for solifenacin once daily at both doses for all domains except personal relationships (Table 1). Table 2 shows that there were many fewer patients included in the analysis of the personal relationships domain than in the other domains. Many (= 40%) patients in each study did not answer the two questions related to sex life, which were required to calculate the personal relationships domain score. This is a common problem with questionnaires that address this aspect of QoL.

Estimated differences from placebo were similar for all active treatment groups when the results from the two 12-week studies were combined. The findings from the primary analysis of both studies were confirmed after adjusting for multiple comparisons in almost all cases. Regression analyses confirmed the validity of the statistical model used for all domains.

Results from 1347 patients from the extension study indicated that both solifenacin 5 and 10 mg provided an improvement in all QoL domains from baseline (start of 12-week studies) to the end of the extension study, which was 17% for the general health perception and 35–48% for all the other domains. Incremental
improvements during the extension study were 28–35% of the total effect obtained from the baseline of the 12-week studies to the endpoint of the extension study. Based on all the QoL domain scores, patients continued to improve throughout the 40 weeks of the extension period (Fig. 1).

At the start of the 12-week studies, patients randomized to placebo had QoL domain scores comparable with those randomized to solifenacin. At the end of the 12-week studies (beginning of the extension study), QoL domain scores for placebo recipients had not improved to the extent they had among solifenacin recipients (Table 2). However, after placebo recipients changed to solifenacin in the extension study, they had improvements in QoL similar to those of patients who had been taking solifenacin during the double-blind studies (Table 2).

**DISCUSSION**

As a chronic, debilitating condition, OAB has a profound negative impact on QoL, including social, physical, psychological, occupational and sexual domains [1,2,20,21]. Many people with OAB stop pursuing the social and physical activities they once enjoyed, and experience seclusion and psychological stress. Embarrassment, frustration, anxiety and depression are common responses to symptomatic OAB [1]. Understanding QoL in patients with OAB is essential to conducting appropriate investigations and to evaluating new interventions, including pharmacological agents [16]. It is desirable that patients have improvements in QoL in parallel with those in efficacy variables.

Based on data from nearly 2000 patients who provided QoL scores from the two double-blind studies and from 1347 patients in the long-term open-label extension study, solifenacin treatment improved the ability of patients to perform daily activities. The lack of statistically significant improvement at the end of the 12-week studies on the personal relationships domain can be explained by the fewer patients completing the questions in this domain. However, it could also be explained by the short duration of treatment, which is interesting because this domain showed an incremental benefit during long-term treatment. This domain particularly might be subject to the effects of adaptive changes over time, as patients become more confident in the improvement in their bladder symptoms, and this confidence is reflected in their interpersonal relations.

The statistically significant improvements in QoL with solifenacin 5 and 10 mg once daily in the double-blind studies were commensurate with those in OAB symptoms. In both 12-week studies, there were significantly fewer urgency episodes, incontinence episodes and voids per 24 h with solifenacin 5 and 10 mg than with placebo. There were also statistically significantly greater mean volumes voided per void in patients receiving solifenacin [9,19]. In addition, the improvements in the incontinence impact domain would appear to correlate with the fewer incontinence episodes per 24 h. A notable finding of the KHQ analysis is the improvement in the sleep/energy domain, which appears to correlate with the improvements in nocturia symptoms seen in patients treated with solifenacin [19].

In the solifenacin extension study, all patients were asked to rate the efficacy and tolerability at each drug-dose assessment visit (weeks 4, 16 and 28). The ratings for efficacy increased at each assessment, from 48% at 4 weeks to 68% at 16 weeks, and to 74% at 28 weeks. These increases in efficacy ratings paralleled the improvements in QoL over time in the extension study.

Tolerability was rated as acceptable or satisfactory for >99% of all patients at all three assessment visits. The favourable tolerability ratings are further supported by the high continuation rates (83% of patients randomized to solifenacin in the double-blind

<table>
<thead>
<tr>
<th>QoL domain</th>
<th>Treatment</th>
<th>N</th>
<th>Change, baseline to endpoint</th>
<th>Change, baseline to endpoint, open-label</th>
</tr>
</thead>
<tbody>
<tr>
<td>General health perception</td>
<td>Placebo</td>
<td>499</td>
<td>-2.3</td>
<td>-7.8</td>
</tr>
<tr>
<td></td>
<td>5 mg</td>
<td>517</td>
<td>-4.3</td>
<td>&lt;0.001 &lt;6.0</td>
</tr>
<tr>
<td></td>
<td>10 mg</td>
<td>527</td>
<td>-6.0</td>
<td>0.031 &lt;7.1</td>
</tr>
<tr>
<td>Incontinence impact</td>
<td>Placebo</td>
<td>498</td>
<td>-18.2</td>
<td>-32.9</td>
</tr>
<tr>
<td></td>
<td>5 mg</td>
<td>518</td>
<td>-24.7</td>
<td>&lt;0.001 &lt;33.5</td>
</tr>
<tr>
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<td>10 mg</td>
<td>528</td>
<td>-27.3</td>
<td>&lt;0.001 &lt;35.3</td>
</tr>
<tr>
<td>Role limitations</td>
<td>Placebo</td>
<td>498</td>
<td>-15.4</td>
<td>-30.8</td>
</tr>
<tr>
<td></td>
<td>5 mg</td>
<td>514</td>
<td>-20.6</td>
<td>&lt;0.001 &lt;29.1</td>
</tr>
<tr>
<td></td>
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<td>526</td>
<td>-22.7</td>
<td>&lt;0.001 &lt;28.9</td>
</tr>
<tr>
<td>Physical limitations</td>
<td>Placebo</td>
<td>497</td>
<td>-13.7</td>
<td>-26.0</td>
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<tr>
<td></td>
<td>5 mg</td>
<td>513</td>
<td>-17.7</td>
<td>0.002 &lt;25.7</td>
</tr>
<tr>
<td></td>
<td>10 mg</td>
<td>525</td>
<td>-20.3</td>
<td>&lt;0.001 &lt;27.0</td>
</tr>
<tr>
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<td>Placebo</td>
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<td>-7.8</td>
<td>-15.7</td>
</tr>
<tr>
<td></td>
<td>5 mg</td>
<td>514</td>
<td>-11.3</td>
<td>0.003 &lt;15.6</td>
</tr>
<tr>
<td></td>
<td>10 mg</td>
<td>523</td>
<td>-11.7</td>
<td>0.015 &lt;18.1</td>
</tr>
<tr>
<td>Personal relationships</td>
<td>Placebo</td>
<td>319</td>
<td>-9.7</td>
<td>-13.2</td>
</tr>
<tr>
<td></td>
<td>5 mg</td>
<td>349</td>
<td>-8.7</td>
<td>0.650 &lt;14.1</td>
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<tr>
<td></td>
<td>10 mg</td>
<td>338</td>
<td>-9.3</td>
<td>0.747 &lt;15.0</td>
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<tr>
<td>Emotions</td>
<td>Placebo</td>
<td>496</td>
<td>-12.3</td>
<td>-21.0</td>
</tr>
<tr>
<td></td>
<td>5 mg</td>
<td>517</td>
<td>-16.0</td>
<td>&lt;0.001 &lt;22.2</td>
</tr>
<tr>
<td></td>
<td>10 mg</td>
<td>526</td>
<td>-17.7</td>
<td>&lt;0.001 &lt;24.8</td>
</tr>
<tr>
<td>Sleep/energy</td>
<td>Placebo</td>
<td>497</td>
<td>-10.0</td>
<td>-18.8</td>
</tr>
<tr>
<td></td>
<td>5 mg</td>
<td>518</td>
<td>-13.8</td>
<td>0.002 &lt;17.9</td>
</tr>
<tr>
<td></td>
<td>10 mg</td>
<td>527</td>
<td>-14.4</td>
<td>0.001 &lt;19.5</td>
</tr>
<tr>
<td>Severity measures</td>
<td>Placebo</td>
<td>493</td>
<td>-7.3</td>
<td>-14.7</td>
</tr>
<tr>
<td></td>
<td>5 mg</td>
<td>516</td>
<td>-10.5</td>
<td>&lt;0.001 &lt;15.3</td>
</tr>
<tr>
<td></td>
<td>10 mg</td>
<td>522</td>
<td>-13.2</td>
<td>&lt;0.001 &lt;17.2</td>
</tr>
<tr>
<td>Symptom severity</td>
<td>Placebo</td>
<td>500</td>
<td>-2.6</td>
<td>-4.7</td>
</tr>
<tr>
<td></td>
<td>5 mg</td>
<td>518</td>
<td>-3.4</td>
<td>&lt;0.001 &lt;4.4</td>
</tr>
<tr>
<td></td>
<td>10 mg</td>
<td>528</td>
<td>-3.6</td>
<td>&lt;0.001 &lt;4.7</td>
</tr>
</tbody>
</table>

© 2005 BJU INTERNATIONAL
The OAB is a chronic, debilitating condition requiring long-term therapy that maintains a positive QoL. Combined data from two 12-week clinical trials supported the use of solifenacin as a safe and effective option for treating OAB symptoms that also statistically significantly enhanced the QoL of the patient being treated. Improvements in QoL with solifenacin continued in the long-term, open-label extension study. The favourable balance of efficacy and tolerability offered by solifenacin for managing the OAB is further supported by the positive findings in health-related QoL reported here, and by the long-term patient satisfaction and persistence.

CONFLICT OF INTEREST

C. Kelleher has received sponsorship to attend meetings and has been involved in symposia for Pfizer, Yamanouchi, Lilley, Novartis and Q Med.

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Correspondence: Con Kelleher, Guys and St. Thomas’ Hospital, London, UK e-mail: Con.Kelleher@gstt.nhs.uk

Abbreviations: OAB, overactive bladder; QoL, quality of life; KHQ, King’s Health Questionnaire.
Quantifying symptoms in men with interstitial cystitis/prostatitis, and its correlation with potassium-sensitivity testing

C. LOWELL PARSONS, MATT T. ROSENBERG*, PEJVAK SASSANI, KAMYAR EBRABHI, JAMES A. KOZIOL† and PAUL ZUPKAS

Division of Surgery/Urology, University of California San Diego Medical Center, San Diego, CA, *Mid-Michigan Health Centers, Jackson, MI and †Division of Biomathematics, Department of Molecular and Experimental Medicine, Scripps Research Institute, La Jolla, CA, USA

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INTRODUCTION

In evaluating a patient with urinary urgency/frequency and/or pelvic pain, it is important to consider all tissues or organs that may give rise to these symptoms. This is straightforward for urgency/frequency, which is primarily generated by the bladder, and for dysuria, which is generated by the urethra, but it is more complicated to identify the origin of pelvic pain. Because the bladder and prostate are visceral organs whose innervation travels back to the spinal cord, pain of bladder or prostatic origin may refer to any location(s) in the pelvis, including the lower abdomen, the lower back, the inguinal area, the scrotum, the testes, the penis, the perineum and (in the female) the labia [1–4]. If a man has only penile and ejaculatory pain, it is reasonable to assume that the pain arises from the prostate, but if he has pelvic pain in other locations, it is equally possible that the bladder is the source.

Patients diagnosed with chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) and patients with interstitial cystitis (IC) have similar symptoms, including urinary urgency/frequency and/or pelvic pain, including pain associated with sexual activity [5–7]. Several investigators have suggested that IC in men is probably under-diagnosed and often misdiagnosed as prostatitis [8–11]. High rates of abnormal bladder epithelial permeability have been detected both in men with prostatitis [4], and in men and women with IC [1,2,12,13], suggesting that the same pathophysiological processes are present. In addition, a recent clinical study showed that men with CP/CPPS [14] had a significant decrease in frequency and severity of symptoms after 3–6 months of therapy with pentosan polysulphate sodium, an oral treatment for IC thought to aid in restoring the normal impermeability of the bladder epithelium [15]. These findings support the notion that IC and male CP/CPPS may be part of a larger disease entity with a common pathophysiology of altered mucosal permeability that might affect the entire lower urinary tract [8,12].

On the basis of extensive basic and clinical research, we hypothesized that most patients with IC have a bladder epithelial dysfunction that allows irritative substances in urine, chiefly potassium, to penetrate the normally impermeable epithelium and provoke symptoms by activating nerves in the underlying tissue [12]. To test for this, we developed the intravesical potassium sensitivity test (PST) [16]. Of >2200 symptomatic patients tested to date, 78% were PST-positive [12]. We also developed and validated the pelvic pain and urgency/frequency (PUF) scale [2] for screening and diagnosing patients with IC. In women with IC and in those with CPPS, the likelihood of a positive PST increases with the PUF score. The positive PST rate was 74% in women with a PUF score of 10–14, 76% in those with 15–19, and 91% in those with ≥20 [2].

The present study was conducted to determine whether men with prostatitis had pathophysiology originating in the bladder, as indicated by a positive PST, and to evaluate the PUF as a predictor of the PST. In addition,
because urethral symptoms are more common in men with IC and/or lower urinary dysfunctional epithelium (LUDE) than in affected women, we conducted KCl irrigation studies before and after experimental urethral mucosal injury, to determine whether urethral potassium cycling caused urethral discomfort in male controls.

**PATIENTS, SUBJECTS AND METHODS**

The study included patients referred to the University of California at San Diego urology clinic who had symptoms of prostatitis, a previous diagnosis of prostatitis, and a history of at least one course of antibiotic treatment for prostatitis; and those presenting to a primary-care clinic in Michigan with symptoms of prostatitis and a history of at least one course of antibiotic treatment for prostatitis. Each centre enrolled both patients with prostatitis and controls. All controls were screened for urological symptoms using the PUF scale, and any potential controls with a score of >1 were excluded. Patients with prostatitis were asked to complete the PUF questionnaire (Fig. 1), an instrument previously reported as validated [2]. All controls and all patients with prostatitis had a PST, as previously described [17].

In a separate group of 22 male controls who did not have a standard PST, a 12 F urethral catheter was placed up to the end of the bulb urethra, taped in position, and the subject asked to rate any urgency or pain provoked by catheterization. The urethra was gently irrigated with KCl (10 mL, 0.2 mol/L) and left in place for 5 min. The urethra was then rinsed with 10 mL water and irrigated with protamine sulphate (10 mL, 5 mg/mL); protamine disrupts the barrier function of the urothelial mucosa [18]. The next part of the study was double-blind; group A was irrigated with 0.2 mol/L KCl and group B with 0.2 mol/L NaCl (11 men each) for 5 min. The subject was then asked to rate his urgency and pain.

### RESULTS

Overall, 64 individuals completed both the PUF questionnaire and had a PST (14 controls, 40 urological patients at San Diego, and 10 in primary care at Michigan). All 14 controls had PUF scores of 0 or 1 and a negative PST. In contrast, all patients with prostatitis had PUF scores of ≥7 and 39 of 50 (78%) were PST-positive (Table 1). The urology patients tended to have higher PUF scores than the primary-care patients (Fisher’s exact test, \( P = 0.034 \)). From logistic regression, neither the PUF score nor group (urology vs primary care) was predictive of PST positivity (difference in deviances 0.47, \( P = 0.98 \)).

The combined female urological and gynaecological patient groups reported previously [2] tended to have higher PUF scores than the combined male urology and primary-care groups with prostatitis (chi-square test, \( P = 0.003 \)). Overall, 80% (262/326) of women were PST-positive, compared with 77% of men (no significant difference between women and men; Fisher’s exact test, \( P = 0.46 \)). Women, but not men, tended to have greater PST positivity with higher PUF score (\( P < 0.001 \) for women; \( P = 0.81 \) for men; Cochran-Armitage test for trend).

In the urethral irrigation study, 22 male controls received KCl (group A) or NaCl (group B) before and after injury of the urethral mucosa with protamine sulfate. All men who reported pain complained of pain in the urethra or the penis, and did not report bladder pain. Before urethral injury, some men reported frequency/urgency associated with placing the catheter, but these symptoms were unaffected by KCl. In group A, three men reported pain and three urgency in response to KCl before urethral injury; after urethral injury, all 11 men reported pain and four urgency in response to KCl. In group B, two men reported pain and four reported urgency in response to NaCl before urethral injury; after urethral injury, none reported pain and two reported urgency in response to NaCl. Thus, after urethral injury with protamine, significantly more men reported urethral pain in response to KCl than to NaCl (Fisher’s exact test, \( P < 0.001 \)) and significantly more men reported pain in response to KCl after urethral injury than before (group A, McNemar’s test, \( P = 0.008 \)).

### DISCUSSION

In the present study, all 50 men with prostatitis scored ≥7 on the PUF scale and 77% had a positive PST. This high rate is similar to the 80.4% rate of positive PST reported in women with IC and patients with CPPS, who had PUF scores of ≥5 (Table 2) [2]. Interestingly, the rates of positive PST were high across all PUF score ranges of ≥7 in men, while the rate of positive PST increased in direct proportion to the PUF score in women [2]. The finding of a positive PST in most patients with prostatitis suggests that, in many such cases, the symptoms might arise from bladder epithelial dysfunction, a pathophysiology that has been detected in many patients with IC [1,2,13].

The bladder epithelial dysfunction in IC results in an abnormally high degree of urothelial permeability [1,2,13]. The principal regulator of epithelial permeability is the bladder surface mucus layer, which contains glycosaminoglycans [16,18–20]. As a result of the mucosal defect, a bladder epithelial leak could allow potentially injurious urinary constituents, primarily potassium, to penetrate the urothelium and depolarize sensory nerves for urgency and/or pain [16]. Once the potassium has penetrated past the mucus barrier, it could then also contribute to neurogenic inflammatory mechanisms [3]. We developed the PST on the hypothesis that an abnormally permeable epithelium would allow urinary potassium to diffuse down the gradient from the high concentrations in urine to the low concentrations in the bladder wall, and thereby lead to the generation of patients’ symptoms [16]. Our early PST studies showed that normal subjects had no sensitivity to intravesical potassium, while
### PELVIC PAIN and URGENCY/FREQUENCY PATIENT SYMPTOM SCALE

Please circle the answer that best describes how you feel for each question.

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>How many times do you go to the bathroom during the day?</td>
<td>3-6</td>
<td>7-10</td>
<td>11-14</td>
</tr>
<tr>
<td>2</td>
<td>a. How many times do you go to the bathroom at night?</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>b. If you get up at night to go to the bathroom, does it bother you?</td>
<td>Never</td>
<td>Occasionally</td>
<td>Usually</td>
</tr>
<tr>
<td>3</td>
<td>a. Do you now or have you ever had pain or symptoms during or after sexual intercourse?</td>
<td>Never</td>
<td>Occasionally</td>
<td>Usually</td>
</tr>
<tr>
<td></td>
<td>b. Has pain or urgency ever made you avoid sexual intercourse?</td>
<td>Never</td>
<td>Occasionally</td>
<td>Usually</td>
</tr>
<tr>
<td>4</td>
<td>Do you have pain associated with your bladder or in your pelvis (vagina, labia, lower abdomen, urethra, perineum, testes, or scrotum)?</td>
<td>Never</td>
<td>Occasionally</td>
<td>Usually</td>
</tr>
<tr>
<td>5</td>
<td>a. If you have pain, is it usually Mild</td>
<td>Moderate</td>
<td>Severe</td>
<td></td>
</tr>
<tr>
<td></td>
<td>b. Does your pain bother you?</td>
<td>Never</td>
<td>Occasionally</td>
<td>Usually</td>
</tr>
<tr>
<td>6</td>
<td>Do you still have urgency after going to the bathroom?</td>
<td>Never</td>
<td>Occasionally</td>
<td>Usually</td>
</tr>
<tr>
<td>7</td>
<td>a. If you have urgency, is it usually Mild</td>
<td>Moderate</td>
<td>Severe</td>
<td></td>
</tr>
<tr>
<td></td>
<td>b. Does your urgency bother you?</td>
<td>Never</td>
<td>Occasionally</td>
<td>Usually</td>
</tr>
<tr>
<td>8</td>
<td>Are you sexually active?</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

**SYMPTOM SCORE** = (1, 2a, 3a, 4, 5a, 6, 7a)

**BORHER SCORE** = (2b, 3b, 5b, 7b)

**TOTAL SCORE** (Symptom Score + Bother Score) =
nearly 80% of the patients with IC had a significant symptomatic reaction [16]; such a reaction to intravesical potassium is a strong surrogate indicator of abnormal epithelial permeability. When the epithelial mucus is normal and healthy it is not possible for urinary potassium to reach sensory nerves, or even the epithelial cell membrane, to trigger responses that would depolarize the nerves. Only a permeability problem could make it possible for potassium to diffuse and result in the generation of symptoms in the bladder. In both men and women, the lower urinary tract includes epithelial tissues that come into contact with urine not only at the bladder surface but also in the urethra and, in men, in the prostatic ducts. The potential exists for an epithelial ‘leak’ and the provocation of symptoms in any of these tissues. Thus the entities termed ‘IC’ and ‘prostatitis’ may be aspects of a single disorder that manifests variably between individuals, and between men and women.

Because pain originating in the bladder can refer to locations throughout the pelvis [1–4], the symptoms of prostatitis in men might arise from a bladder epithelial leak. Urethral or prostatic epithelial leaks could also generate symptoms. The present findings indicate the presence of urethral and bladder components in the men assessed here. Although a prostatic component may be present, it is not scientifically proven.

Men with IC/LUDE are more likely to have urethral symptoms than are women with the disease [1,4], possibly because the male urethra is longer. The results of urethral irritation in the present study support the hypothesis that urethral symptoms are provoked by an epithelial potassium leak. In the present studies of male controls whose urethral epithelia had been injured with protamine, urethral pain was reported by all men who had urethral KCl irrigation, and by none who had urethral NaCl irrigation. There were no significant between-group differences in the number of men reporting urgency before and after mucosal injury. This supports the concept that urgency is a bladder symptom, while the origin of pelvic pain other than dysuria is less obvious.

The diagnostic tests that are necessary or desirable in the differential diagnosis of IC/LUDE are a subject of continuing debate. The value of cystoscopy in diagnosing IC was questioned in 1998 [21], when healthy women undergoing tubal ligation were found on cystoscopy to have the same mucosal lesions as patients with IC. In another study, Novicki et al. [22] detected IC in 48% (14/29) of men diagnosed with prostatitis and concluded that cystoscopy with hydrodistension is necessary for the diagnosis of IC in men. Although IC/LUDE is under-diagnosed and often misdiagnosed, we think that using the PUF and PST is sufficient to differentiate the disease from other urological and gynaecological disorders.

The present data indicate that the PUF score is a strong predictor of PST outcome in patients with prostatitis, and in women with IC or CPPS. Although the PST is useful in the diagnosis of IC/LUDE [12], it is desirable to have an alternative way of screening for the disease in men, because urethral catheterization is more difficult in men than in women, and the urethra is also involved in the disease process. For these reasons, using the PUF questionnaire as a noninvasive and easily administered proxy for the PST should be considered in men with symptoms of CP/CPPS.

The present findings suggest that pathology originating in the bladder may be an important source of symptoms in many men diagnosed with prostatitis. In addition, the PUF questionnaire appears to be a strong predictor of PST positivity in men with prostatitis. Although prostatitis and IC have been considered two distinct disease entities, they may be part of a continuum of epithelial permeability and potassium cycling in the lower urinary tract. The finding that potassium causes pain in the experimentally injured male urethra suggests that urethral symptoms can arise from abnormal epithelial permeability and potassium cycling in urethral tissues.

**CONFLICT OF INTEREST**

None declared.

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Correspondence: C. Lowell Parsons, c/o Miriam Seva, Division of Urology, University of California San Diego Medical Center, 200 West Arbor Drive, San Diego, CA 92103–8897, USA. e-mail: mseva@ucsd.edu

Abbreviations: CP/CPPS, chronic prostatitis/chronic pelvic pain syndrome; IC, interstitial cystitis; LUDE, lower urinary dysfunctional epithelium; PST, potassium sensitivity test; PUF, pelvic pain and urgency/frequency.
A prospective, double-blind, randomized cross-over study evaluating changes in urinary pH for relieving the symptoms of interstitial cystitis

CHRISTOPHER NGUAN, LUIGI G. FRANCIOSI*, NOAM N. BUTTERFIELD*, BERNARD A. MACLEOD†, MARTHA JENS and HOWARD N. FENSTER

UBC Division of Urology, VGH, Clinical Pharmacology Research Organization, Pharmacology & Therapeutics, and †Anaesthesia and Pharmacology & Therapeutics, Vancouver, BC, Canada

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OBJECTIVE

To provide evidence for the clinical efficacy of changes in urinary pH on the pain associated with interstitial cystitis (IC).

PATIENTS AND METHODS

A prospective, randomized, double-blind cross-over study was conducted with 26 women with IC between 2000 and 2002, consisting of cross-over instillations of urine at physiological pH (5.0), and neutral buffered pH (NaH₂PO₄, buffered to pH 7.5). The outcome measured was the subjective symptom of pain assessed using a visual analogue scale at baseline, after the initial instillation of solution, at washout, and after the crossover instillation. Data were analysed using repeated-measures analysis of variance.

RESULTS

There was no statistically significant difference between the mean (SD) change from baseline pain scores after instilling neutral buffered solution, at 0.50 (2.78), and acidic solution, at 0.33 (3.43) (P = 0.85). Secondary outcomes were analysed, including baseline variability and treatment-order effects; neither were significantly different between the groups.

CONCLUSIONS

There was no statistically significant difference in subjective pain scores on instilling urine at physiological pH or sodium-phosphate buffered saline in these patients with IC. Further work is required to define the role, if any, of urinary pH in the pathophysiology and treatment of IC.

KEYWORDS

interstitial cystitis, pH, pain, alkalinization

INTRODUCTION

Interstitial cystitis (IC) is a chronic, debilitating urological condition affecting both young and old. The symptom complex consists of suprapubic and/or pelvic pain with associated irritative voiding symptoms, including dysuria, frequency, nocturia and urgency. IC is a diagnosis of exclusion and may represent the end-organ effects of several different pathways of progressive insult to the urinary tract. Although thought to be quite prevalent, it has been difficult to establish epidemiological values for IC, because of the inability to establish both strict and functional criteria in the diagnosis of this disease. Diverse urogynaecological conditions, chronic pelvic pain and systemic inflammatory/pain syndromes (fibromyalgia, etc.) may overlap with the symptoms of IC [1]. Although good research is currently being conducted on IC, chronic pelvic pain, infectious disease and neuroendocrine disease, the exact causes of IC remain to be elucidated. As such, treatment algorithms to date remain empirically based and await clinical trials to determine their efficacy [2–6].

Pre-clinical work in anaesthesia, clinical pharmacology and the neurosciences show that neural modulation and transmission of pain are accentuated by direct stimulation in low pH environments [7–10]. Indeed, studies on exposure of model bladders (rat and guinea pig) to instillations of low pH solutions show dynamic changes in the bladder urothelium, leading to transient increases in permeability to various ions, including potassium, hydrogen and fluoride [9]. These permeability changes may occur via specific membrane bound ‘pores’ which become activated (transcellular), or via changes in desmosome-mediated cell-cell contact (pericellular). The mechanisms by which increased flux of inappropriate ions cause pain is not yet clear, but studies of bladders from patients with IC show increases in substance P transcription (a known excitatory pain afferent mediator) and theoretical actions of direct neuronal damage or depolarization, possibly involving instigators of inflammation such as prostanooids [11].

Anecdotally, alkalinizing agents in managing cystitis-like symptoms (frequency, urgency, dysuria) have been used over the past 20 years or more; up to half of patients presenting with cystitis-like symptoms will have no bacteriuria on urine culture. Previously these patients have been offered treatment with potassium citrate, sodium citrate or sodium bicarbonate, generally on the basis of anecdotal evidence and with a quoted symptom improvement rate of up to 80% [12,10]. A more recent study re-evaluated the relationship between urinary pH and cystitis symptoms, concluding that there was no relationship between them for a pH of 5.0–8.0, and no correlation between urinary pH in symptomatic patients at initial presentation who were asymptomatic on follow-up [12]. This particular report did not address alkalinization of the urine specifically, but instead extrapolated the findings accordingly. The investigators pooled both
bacteriuric and abacteriuric patients for analysis, which would invalidate the study for comparing patients with IC, who must be deemed to have negative urine cultures.

In the present study we sought to determine the effects of altering intravesical pH on the symptoms of patients known to have IC. A neutral buffered solution, consisting of sodium phosphate, was compared with an acetic-acid buffered solution, the study providing a basis for possible further investigations in the area of pH in relation to clinical IC, and as such seeking to maximize the effect by directly administering both an acidic saline solution (pH 5.0) and a neutral buffered saline solution (pH 7.5) in a crossover design trial.

PATIENTS AND METHODS

Three hundred patients with IC were notified of the opportunity to participate in the study, through a letter of introduction given to all urologists in the province of British Columbia and by contacting the Interstitial Cystitis Society of British Columbia. Patients who expressed an interest in participating in the study were given an information sheet outlining the study and a consent form. The principal investigator or study nurse then interviewed patients to determine their eligibility, by using the National Institutes of Health inclusion and exclusion study criteria for IC [13]. The mean duration of IC symptoms for the study population was 3 years; the number of patients who either refused to participate or withdrew from the study was recorded, with their reasons.

The calculated sample size required for this study was 40 patients, or 20 patients per group, determined using a variance estimate obtained from a pilot study. Finally 26 patients (all female) were recruited at the predetermined date of closure of the study. The low accrual rate was attributed mainly to patients’ reluctance to possibly exacerbate their condition.

After obtaining informed consent, each patient was randomly assigned to one of two groups: group 1 received a gravity-driven instillation of 100 mL of acidic-buffered solution (pH 5.0) followed by 100 mL of neutral buffered solution (pH 7.5; NaH₂PO₄ buffered); and group 2 a similar instillation of 100 mL of neutral buffered solution (pH 7.5; acetic-acid buffered) followed by 100 mL of acid-buffered solution (pH 5.0). Before instilling the first solution, baseline pain was measured using a 10-point numerical rating scale (NRS). Immediately after obtaining the baseline pain scores, the patient’s urethra was lubricated, a 12 F catheter inserted into the bladder, and the first solution instilled. After 30 min the patient was asked to rate their pain. The bladder was then drained and washed twice with sterile distilled, de-ionized water, after which the patient was again asked to rate their pain. The second solution was then instilled and the final pain score measured 30 min later (Fig. 1). The effluent drained from the patients’ bladders was discarded appropriately.

All patients were randomly assigned to groups 1 or 2 on the study day and all received both acid and neutral-buffered solutions. A balanced design with equal numbers of patients receiving high or low pH first (in blocks of four) was generated using appropriate software. Both the patients and researchers were unaware of the contents of each solution given.

The NRS scores were first analysed using descriptive statistics. Baseline NRS scores were subtracted from those obtained after instilling the assigned solution. Means and CIs were calculated, and a repeated-measures ANOVA then conducted. The null hypothesis was that there was no difference between NRS scores of patients after the sequential instillation of each solution into the bladder for 5 min. The alternative hypothesis was that there was a significant difference. An α of 0.05 and β of 0.80 were used to assess statistical significance. The secondary variables were analysed statistically, being only intended to help describe the primary outcome.
RESULTS

There was no statistically significant difference between the mean change from baseline pain scores (NRS) after instilling the neutral buffered solution, with mean (SD) range (values of 0.50 (2.78, -7 to 5) and 0.33 (3.43, -9 to 7), respectively (P = 0.85). For the secondary outcome measure, the baseline NRS scores changed in both groups of patients, by -0.12 (2.71, -7 to 4) with neutral solution first, and 1.15 (3.72, -5 to 9) with acidic solution first, although in no predictable direction or magnitude (Table 1).

To minimize the influence of possible carry-over effects and treatment-by-period interactions, we analysed the difference between NRS scores before and after treatment in the first period. There were no significant changes in pain scores between the two groups, at, -0.08 (2.84, -7 to 3) and -0.27 (4.37, -9 to 7), respectively.

To determine if there were any significant order effects, the change in pain scores before and after treatment was assessed for the first and second treatment for each solution. There was no detectable difference in the change in NRS score after the first and second instillation of the neutral solution, at, -0.08 (2.84) and 1.08 (2.69), respectively, nor after the first and second instillation of the acidic solution, at, -0.27 (4.37) and 0.92 (2.14), respectively.

DISCUSSION

There was no difference in change from baseline pain scores between bladder instillations of an acid-buffered and that of a neutral pH solution in patients with IC. The direction of change (degradation or improvement) in pain ratings was also inconsistent between the groups, and thus we cannot speculate as to whether there would have been a significant difference in response between the groups with more participants.

The study was closed at a predetermined time limit, with only 26 patients recruited, less than the expected 40. Despite these few patients the study was adequately powered to detect a minimum difference of 1.7 in NRS scores, a difference that would be considered clinically significant. The power to detect the difference actually found, 0.17, was <5% but even if enough patients were recruited to achieve a power of 80% (estimated at 1926 patients) a difference this small would probably not be clinically relevant. Thus, despite the few patients the absence of an effect probably represents clinical reality.

The change in baseline scores within the two groups was insignificant. Again, there were changes in both magnitude and direction in both groups. Although the baseline shift did not become a significant factor in the study, the data were analysed only in the first half of the study, before the crossover, as a strategy to eliminate the issue of repeated baseline pain measures; there was no significant relationship between them.

Further review of the data failed to show any exacerbation in NRS scores with the instillation of an acid-buffered solution. As discussed, previous reports suggested that direct application of an acidic environment to afferent pain receptors causes exacerbation of pain. Hohbrugger and Lentsch [9] showed a decrease in rat bladder capacity with a pH of 8 and low osmolality, suggesting that intravesical ions can permeate the mucosal epithelium and affect nerves, muscle fibres or both. Although Hohbrugger and Lentsch did not assess pain responses, as their study animals were anaesthetised, there would probably be changes in pain sensation based on these changes in ionic values and intravesical ion flux across the bladder mucosa. Technical considerations might be why there was no detectable pain score difference in the present study with the instillation of acidic solution, in that the duration of instillation may be significant and possibly underestimated. With increases in duration there were corresponding increases in ion flux in the earlier study [9], and although the present study sought to recreate a similar duration of instillation and pH, it is possible that there are differences between rodent and human bladder absorption kinetics that are not yet appreciated. Again, this is an area of potential further study.

To our knowledge, the present study represents only the third such to investigate the effects of changes in urinary pH on the human clinical symptom profile, and the first in patients with IC. In their discussion, Hohbrugger and Lentsch [9] suggested that changes in intravesical pH affect not only transcellular and pericellular transport and leakage of ions and osmolytes, but also a subepithelial countercurrent exchange mechanism, similar to that of the kidney. Cellular equilibrium is established in the bladder mucosa and submucosa with the intravesical fluid, thus limiting absorption through the bladder lining [9,14–16]. Changes in this equilibrium may allow increased transmission of reactive species through the bladder mucosa to stimulate the onset of LUTS. Andersson [2,17], in recent reviews of the mechanisms of bladder afferent excitability, postulated several inducible mediators of C-fibre stimulation in the bladder urothelium. Thus, in the light of previous discussions, perhaps direct stimulation of this nerve complex of pain-transmitting C-fibres by pH-dependent urothelial leak or pH-stimulated inducible mediators may be responsible for reproducible pain with agents which acidify the urine. The converse would hold, that treatments which seek to alkalize the urine would negate these untoward effects. Possibly these effects would be heightened in patients with IC, secondary either to increased afferent excitability, or to pathophysiological changes of the bladder urothelium.

We examined intravesical alkalization in the context of neutralising a pre-existing relatively acidic state. Further work could examine clinical symptom changes with alkaline intravesical environments of pH ≥ 8.0. A titration or dose-response study would be invaluable in assessing both high and low intravesical pH ranges which affect reproducible changes in clinical symptoms. After this, focused studies relating to oral buffer administration and subsequent urinary pH effects would help to guide clinical practice.

**TABLE 1** The change in baseline pain scores (NRS)

<table>
<thead>
<tr>
<th>Change, n</th>
<th>Neutral pH (7.5)</th>
<th>Low pH (5.0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Decreased</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Unchanged</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>13</td>
<td>13</td>
</tr>
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ACKNOWLEDGEMENTS

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CONFLICT OF INTEREST

None declared. Source of funding: Interstitial Cystitis Association USA.

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Correspondence: Howard Fenster, D-9 Heather Pavillion, VGH, 2733 Heather Street, Vancouver, BC V5Z 3JS, Canada.
e-mail: howardfenster@shaw.ca

Abbreviations: IC, interstitial cystitis; NRS, numerical rating scale.
Groin pain after a tension-free vaginal tape or similar suburethral sling: management strategies

JONATHAN R.A. DUCKETT and SMITA JAIN
Department of Obstetrics and Gynaecology, Medway Maritime Hospital, Gillingham, Kent, UK
Accepted for publication 3 August 2004

OBJECTIVE
To review different treatment strategies for women with groin pain after tension-free vaginal tape (TVT) or similar suburethral sling procedures.

PATIENTS AND METHODS
The series comprised 450 women who had a TVT procedure, with a follow-up of 3–50 months. Five women (1%) reported significant groin pain and were offered further treatment. In addition, one woman was referred from another centre and received treatment.

RESULTS
Women with pain were initially treated conservatively, and in most the pain resolved and required no further treatment. Persistent or severe discomfort was treated with a combined steroid (methyl prednisolone, 2 mL, 80 mg) and local anaesthetic (bupivacaine, 10 mL, 0.5%) injection in four women. There were no side-effects from the treatment. One woman was relieved of her pain and required no further treatment. In one woman the local injections failed to improve her symptoms but the pain was not severe enough to warrant further treatment. Two women developed recurrent pain after an initially successful injection, and in these women the TVT was excised. One woman referred from another centre was primarily treated with TVT excision. In the three women treated with distal tape excision, the mean pain scores decreased from 8.7 before excision to 0.7 afterward. One woman is awaiting tape excision.

CONCLUSION
If conservative management fails to relieve the symptoms of groin pain it can be treated by injecting a mixture of steroid and local anaesthetic. However, local injection failed to provide long-term relief in three of four women. More severe symptoms might require TVT mesh dissection and excision, which provided significant pain relief.

KEYWORDS
tension-free vaginal tape, pain, stress incontinence, adhesions.
In three women the distal end of the tape (∼5 cm) was excised from the level of the top of the symphysis to the insertion into the skin, under general anaesthesia. Two women were treated in the day-case unit, but one had travelled a considerable distance for treatment and was kept in hospital overnight after surgery. Cystoscopy was normal in all of these women. The patient was placed in the dorsal lithotomy position with vaginal/perineal preparation and draping. An oblique incision was made over the area of maximum tenderness. The pubic tubercle and superficial inguinal ring were identified and an area between the skin and upper border of the symphysis explored. The tapes were encased in adhesions, forming a thick, cord-like structure, with strands of the polypropylene mesh visible in the surface. The Cave of Retzius was explored in one woman after difficulty in identifying the tape. Two women had previously had a TVT, and one woman had an intravaginal slingsplasty (IVS, Tyco, Gosport, UK) as the primary surgery. The woman with the IVS had bilateral groin incisions and tape excision because of bilateral pain. The women were given broad-spectrum antibiotics during surgery, and pain scores were assessed before and after surgery (on a scale from 0 to 10, where 0 is no pain at all, and 10 the most severe pain imaginable).

RESULTS

The four women were initially cured of their pain by the local injection, but there was no sustained benefit for longer than 6 weeks in three of the women. One woman failed to improve with an injection of local anaesthetic and steroid, but did not consider her pain severe enough to warrant further major intervention.

In all women who had the TVT excised, the tape was encased in adhesions medial to superficial inguinal ring. The tape curled around from the back of the pubic symphysis down into the mons pubis. In one woman, traction on the tape caused the skin of the mons to pucker (Fig. 1), and she complained primarily of suprapubic pain. In another woman, traction on the tape caused the skin of the vagina to pucker, and she complained of both vaginal and suprapubic pain.

There were no side-effects from the steroid/local anaesthetic injection, and all women had an uneventful recovery after surgery and remained continent. In the three women who had the TVT excision, the mean pain scores reduced from 8.7 to 0.7.

DISCUSSION

This is the first case series of persistent groin pain not related to posture reported after mid-urethral sling procedures. TVT is gaining popularity as a treatment for women with stress incontinence; it is minimally invasive, quick and with a short hospitalisation and few complications after surgery, and good long-term continence rates [4,5]. Groin pain after TVT seems relatively rare [6,7]; the exact incidence of mild groin pain is difficult to determine, as a history of pain may not be volunteered, or may be dismissed at the initial follow-up visit as normal healing. In the present series, two women presented at >1 year after their initial surgery. Persistent pain will not be identified if women are discharged too soon from follow-up; the follow-up consultation should include a question about groin pain.

Growden and Lebherz [12] suggested that wide displacement of Pereyra suspension sutures could entrap the genitofemoral branch of the ilio-inguinal nerve, causing suprapubic pain; Galloway et al. [13] coined the term ‘post–colposuspension syndrome’ in 1987, and described chronic suprapubic pain after colposuspension that could occur on either or both sides. The pain was mostly in the groin and occurred in six women in a series of 50 colposuspensions. Most of these patients were treated by releasing the colposuspension suture on the affected side.

One cause of groin pain after TVT might be inflammation and oedema of the ilio-inguinal and/or genitofemoral nerves near the iliopectineal ligament [10,11]. Alternatively, the groin pain may be caused by entrapment of the ilio-inguinal nerve, as Miyazaki et al. [14] described similar pain after needle-suspension procedures. The diagnosis is confirmed by the disappearance of the pain after injecting local anaesthetic at the point of maximum tenderness. This might be the cause of pain in one of the present women, who was cured after infiltrating steroid and local anaesthetic. The anatomy of the ilio-inguinal nerve makes it susceptible to entrapment near its exit from the superficial inguinal ring, which lies almost directly above the pubic tubercle. The differential diagnosis of groin pain also includes the possibility of anatomical variation of the ilio-inguinal and genitofemoral nerves. This has implications for surgeons operating in the groin region and for those caring for the patient with groin pain [15]. The intensity of symptoms probably depends on the degree of nerve compression. The pain may last for several weeks, and is gradually replaced by numbness as the nerve degenerates. Surgical treatment for nerve entrapment includes resection or neurolysis in the groin [16]. This can be done using a differential nerve block by local anaesthetic to identify the likely neural origin of the pain. The nerve block might also act therapeutically, as nerve entrapment is usually self-limiting. After diagnosis, the patient should be reassured that usually nerve entrapment will resolve spontaneously.

The three women in the present series who needed TVT excision had persistent pain, making nerve entrapment less likely. If the pain is severe and incapacitating or prolonged, dissection and division of the polypropylene mesh should be considered. It is possible that dissecting the polypropylene sling has the same effect of resection/neurolysis of the ilio-inguinal or genitofemoral nerve in the groin.

The pain might not be caused by nerve entrapment or irritation, but could be...
secondary to adhesions, and structural adhesions may explain why the pain is sometimes positional. If the tape is adherent at one point, movement of the tape at another site might result in abnormal physical distortion of the tissues and pain. Hilton et al. [9] reported pain after TVT related to posture; their cases related to unrecognised urinary tract perforations, and the excision of a portion of an abnormally-positioned tape relieved the pain in two women. This problem is not unique to the Ethicon (TVT) tape that was used for most women, as a similar pain was encountered in a patient with a Tyco tape (IVS). Both tapes use a polypropylene mesh, and it is difficult to compare weave characteristics from the literature provided with the devices. Different meshes might be more or less likely to cause pain, depending on the likelihood of adhesions, and this might partly depend on the mesh weave characteristics.

Previous surgery might increase the risk of adhesions. One patient who had her tape excised had had several previous operations that might have resulted in adhesions (failed vaginal hysterectomy, abdominal hysterectomy, anterior repair, repair of damage to bladder, oophorectomy). Similarly, one woman reported by Hilton et al. [9] had been treated with two anterior repairs before the TVT insertion that caused her pain.

In conclusion, groin pain is a complication of the TVT procedure, with an estimated incidence of ~1%. The incidence may be greater than this, but this symptom may not be readily volunteered. Groin pain can be treated with combined steroid injection and local anaesthetic, but the effect may be transient. Persistent pain is best treated with excision of the distal end of the tape. Although few patients were studied, groin pain was significantly reduced by tape excision.

CONFLICT OF INTEREST

None declared.

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Correspondence: Jonathan R.A. Duckett, Medway Maritime Hospital, Windmill Road, Gillingham, Kent ME7 5NY, UK. e-mail: jraduckett@hotmail.com

Abbreviations: TVT, tension-free vaginal tape; IVS, intravaginal slingplasty.
Managing patients with an overactive bladder and glaucoma: a questionnaire survey of Japanese urologists on the use of anticholinergics

KUMIKO KATO, KAZUHIKO YOSHIDA, KOICHI SUZUKI, TATSURO MURASE and MOMOKAZU GOTOH*
Department of Urology, Japanese Red Cross Nagoya First Hospital, and *Department of Urology, Nagoya University Graduate School of Medicine, Nagoya, Japan
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OBJECTIVES
To establish the views of urologists on the use of anticholinergic drugs for treating the overactive bladder (OAB) in patients with glaucoma.

SUBJECTS AND METHODS
In February 2004 a self-description questionnaire was mailed to all 417 urologists who were members of the Tokai Society of Voiding Dysfunction, to determine current practice in Japan for patients with an OAB and glaucoma. Subgroups were analysed between the types of practice and the duration since the urologists had graduated from medical school.

RESULTS
Of the 155 respondents, 76 (49%) routinely enquired about a history of glaucoma before prescribing anticholinergics, and 45 (29%) routinely referred patients with such a history to ophthalmologists. To treat patients with OAB and glaucoma, 102 (66%) would prescribe anticholinergics if permission were available from the ophthalmologist, 33 (21%) chose other treatments and 17 (11%) abandoned treatment. Forty-nine urologists (32%) were currently prescribing anticholinergics to patients with glaucoma. As to knowledge about glaucoma, 132 (85%) urologists knew that there were two types of glaucoma and 98 (63%) knew about laser iridotomy. The proportion of urologists who knew of the two types of glaucoma and asked patients for this information was significantly higher in university than in general hospitals (P < 0.05).

CONCLUSIONS
Although anticholinergic drugs can precipitate angle-closure glaucoma by pupillary block, they are not contraindicated in open-angle glaucoma or in angle-closure glaucoma that has already been treated by laser iridotomy. Not all urologists are aware of this difference, at least in Japan. Some urologists avoid anticholinergics in all patients with glaucoma, while others pay little attention to glaucoma. Routine history taking and referral to ophthalmologists allows many patients with OAB and glaucoma to benefit safely from anticholinergics. Moreover, clinicians should be aware of patients with OAB who have not been evaluated by ophthalmologists but who are at risk of angle-closure glaucoma.

KEYWORDS
overactive bladder, glaucoma, anticholinergics, questionnaire

INTRODUCTION
For many years, anticholinergic medications have been the main treatment for urgency, frequency and urge incontinence, all of which are symptoms of the disorder currently termed the ‘overactive bladder’ (OAB) [1,2]. Although OAB and glaucoma are common, with an individual and coexistent prevalence higher in the elderly [3,4], the instructions provided with anticholinergics often state that the generalized term ‘glaucoma’ is a contraindication, without specifying the mechanism of drug-induced angle-closure glaucoma [5]. This statement is confusing to both clinicians and patients, and deprives many patients with OAB and a history of glaucoma of the most suitable drug treatment. We conducted a postal survey to investigate the views of urologists on the use of anticholinergics in patients with OAB and glaucoma.

SUBJECTS AND METHODS
In February 2004, a self-description questionnaire with 10 questions was mailed to all members of the Tokai Society of Voiding Dysfunction, who were urologists practising in the Tokai area of Japan. The following information was obtained: (i) the type of practice; (ii) the duration since graduating from medical school; (iii) whether they knew that information provided with packages of anticholinergics used for OAB treatment describe glaucoma as a contraindication; (iv) whether they ascertained a history of glaucoma routinely before prescribing anticholinergics; (v) whether they routinely refer patients with OAB and glaucoma to ophthalmologists; (vi) whether they ask patients about their type of glaucoma; (vii) their choice of OAB treatment for patients with glaucoma; (viii) whether they were currently prescribing anticholinergics to patients with glaucoma; (ix) whether they knew about the two types of glaucoma (open-angle and angle-closure); and (x) whether they knew about laser iridotomy for angle-closure glaucoma. Additional comments provided by the urologists were also analysed. Subgroup for questions iii–x were analysed by comparing responses between grade of staff (senior and junior) and types of practice (private, general hospital, and university hospital). As the status of staff is not
consistent among Japanese hospitals, urologists who had graduated from medical schools >10 years previously were defined as senior staff. The statistical significance of differences at the two-sided 0.05 level was determined using Fisher's exact probability test.

RESULTS

Completed questionnaires were received from 155 of the 417 urologists (response rate 37.2%), most of which (118, 76.1%) were senior staff. Ninety urologists (58%) were working in general hospitals, 34 (22%) in university hospitals, and 31 (20%) were in private practice. The results of subgroup analysis are listed in Table 1.

All but one respondent (99%) knew that information provided with packages of anticholinergics used for OAB treatment describe glaucoma as a contraindication. About half the urologists (49%) routinely took a history of glaucoma before prescribing anticholinergics, half (45%) did this sometimes, and 10 (7%) did not. Forty-five urologists (29%) routinely referred OAB patients with glaucoma to ophthalmologists, 70 (45%) sometimes referred them, and 40 (26%) did not refer them. Thirty-four urologists asked patients about types of glaucoma, and the percentage of urologists doing this was significantly higher in university than in general hospitals (P = 0.01). Many respondents commented that patients do not know what type of glaucoma they have.

For OAB treatment in patients with glaucoma, 103 (67%) of the urologists prescribed anticholinergics if the permission of ophthalmologists was available, 34 (22%) chose other treatment options, and 17 (11%) abandoned treatment. For other treatment options, 11 respondents used herbal medicine (Chinese medicine), seven used flavoxate, one used a-1-blockers, one used imipramine, and three used a-blokaage. Forty-nine urologists (32%) were currently prescribing anticholinergics to patients with glaucoma.

In all, 132 urologists (85%) knew that there were two types of glaucoma, and 98 (63%) knew that laser iridotomy was used on angle-closure glaucoma. The percentage of urologists who knew that there were two types of glaucoma was significantly greater in university than in general hospitals (P = 0.02). Junior staff had a better knowledge of glaucoma than did senior staff, in terms of the existence of two types of glaucoma and the use of laser iridotomy (not significantly different: P = 0.07, 0.08).

DISCUSSION

Official population projections indicate that, because of the low fertility rate, the percentage of elderly (265 years) in Japan will increase from 17.4% in 2000, to 25% in 2014, and will reach 36% in 2050. Such rapid population ageing increases the impact of diseases that impair the quality of life of the elderly. In November 2002 the Neurogenic Bladder Society conducted a nationwide, population-based questionnaire survey to obtain reliable epidemiological information on LUTS in Japan. If OAB is defined as a clinical condition in which the urinary frequency is at least eight voids per day, and urinary urgency occurs at least once per week, the prevalence of OAB in Japanese aged 240 years is 12.4%, of which 6.4% have urge incontinence (more than once per week) [3]. This prevalence of OAB in Japan is only slightly lower than that in the USA and Europe (both 16.6%) [6,7]. The Japan Glaucoma Society conducted a population-based screening of glaucoma (the Tajimi Study) during 2000 and 2001. The prevalence of glaucoma in Japanese aged ≥40 years was estimated at 5.8% (3.9%) with open-angle glaucoma, 1.1% with angle-closure glaucoma, and others, which is even higher than that of Caucasians [4]. As both OAB and glaucoma increase with age, many elderly will have both conditions.

Anticholinergic drugs are the most effective agents currently available to control OAB symptoms. As parasympathetic cholinergically mediated innervation is the predominant stimulus for bladder contraction, anticholinergics can improve frequency, urgency and urge incontinence by blocking receptors of the detrusor muscle. The most common side-effects of anticholinergics are dry mouth, constipation and blurred vision. Anticholinergics can theoretically induce angle-closure glaucoma by narrowing the angle of the anterior chamber, by pupillary dilatation, and by forward movement of the iris/lens diaphragm (pupillary-block glaucoma) [5]. Propiverine and oxybutynin are anticholinergics licensed in Japan for treating OAB, and the instructions provided with them (as well as those provided in many other countries) describe glaucoma as a contraindication but without specifying the type. This description can be misleading to GPs, urologists, pharmacists and patients, who generally know less about glaucoma than ophthalmologists.

<table>
<thead>
<tr>
<th>Question</th>
<th>Junior Staff</th>
<th>Senior Staff</th>
<th>P</th>
<th>Private Practice</th>
<th>General Hospital</th>
<th>University Hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td>Know that package inserts describe glaucoma as a contraindication?</td>
<td>37 (100)</td>
<td>118 (97)</td>
<td>1.00</td>
<td>31 (100)</td>
<td>89 (99)</td>
<td>34 (100)</td>
</tr>
<tr>
<td>Routinely enquire about glaucoma?</td>
<td>20 (54)</td>
<td>56 (48)</td>
<td>0.57</td>
<td>20 (65)</td>
<td>39 (43)</td>
<td>17 (50)</td>
</tr>
<tr>
<td>Routinely refer glaucoma patients to ophthalmologists?</td>
<td>12 (32)</td>
<td>33 (28)</td>
<td>0.68</td>
<td>7 (23)</td>
<td>26 (29)</td>
<td>12 (35)</td>
</tr>
<tr>
<td>Ask patients about their type of glaucoma?</td>
<td>10 (27)</td>
<td>24 (20)</td>
<td>0.49</td>
<td>7 (23)</td>
<td>14 (16)</td>
<td>13 (38)*</td>
</tr>
<tr>
<td>Prescribe anticholinergics with ophthalmologists' permission?</td>
<td>21 (57)</td>
<td>82 (70)</td>
<td>0.17</td>
<td>19 (61)</td>
<td>60 (67)</td>
<td>24 (71)</td>
</tr>
<tr>
<td>Currently prescribing anticholinergics to patients with glaucoma?</td>
<td>10 (27)</td>
<td>39 (33)</td>
<td>0.55</td>
<td>10 (32)</td>
<td>30 (33)</td>
<td>9 (27)</td>
</tr>
<tr>
<td>Know about the two types of glaucoma?</td>
<td>35 (95)</td>
<td>96 (81)</td>
<td>0.07</td>
<td>26 (84)</td>
<td>72 (80)</td>
<td>33 (97)*</td>
</tr>
<tr>
<td>Know about laser iridotomy?</td>
<td>28 (76)</td>
<td>70 (59)</td>
<td>0.08</td>
<td>20 (65)</td>
<td>57 (63)</td>
<td>21 (62)</td>
</tr>
</tbody>
</table>

General vs university hospital urologists, *P* = 0.01 and 10.02; all other comparisons between practice types insignificant, P > 0.05.
Glaucoma is a heterogeneous group of diseases that have in common a characteristic optic neuropathy and visual-field defects, for which elevated intra-ocular pressure is the major risk factor [5]. Intra-ocular pressure depends on the steady-state balance between the formation and drainage of the aqueous humor. An obstruction in the circulatory pathway of the aqueous humor elevates intra-ocular pressure by two main mechanisms: (i) open-angle glaucoma results from increased resistance to aqueous outflow in the trabecular meshwork/Schlemm’s canal system, probably through cellular changes and the accumulation of extracellular material; and (ii), angle-closure glaucoma results from narrowing or closure of the anterior chamber caused by the forward bowing of the iris, thus obstructing outflow of aqueous humor through the trabecular meshwork/Schlemm’s canal system. Open-angle glaucoma, by definition, does not predispose to angle closure. When angle-closure glaucoma is diagnosed by ophthalmologists, laser iridotomy is used to prevent further attacks, by creating an alternative pathway for the aqueous humor; then anticholinergics can be safely administered. The present survey revealed that not all urologists are aware of these features of glaucoma. Younger doctors and those working in university hospitals appeared to have a better knowledge of glaucoma, which suggests an influence of the recent change in Japanese medical education to attach importance to primary care, including minor specialities.

Although it was well known that the package inserts of anticholinergics used to treat OAB describe glaucoma as a contraindication, the information provided with packages of anticholinergics was rather high in the Japanese, especially in women, consistent with other reports that the effects on intra-ocular pressure in the elderly, indicating that the incidence of drug-induced glaucoma increases with age; angle-closure glaucoma occurs in 1 : 100 Caucasians, in 1 : 10 Asians, and in 1 : 100 Mongoloids and Hispanics, and in 2–4 : 100 Inuits [5]. The incidence of drug-induced cases is uncertain [5], but the mydriatic effect of systemically administered anticholinergics is much smaller than that of dilating eye drops used for diagnostic purposes. Sung et al. [10] reported one case of an 80-year-old woman with acute angle-closure glaucoma precipitated by oxybutynin. In Japan, three cases of glaucoma attack related to propiverine have been reported, all of which were elderly women (73, 88 and 88 years old) with no history of glaucoma (Taiho Pharmaceutical Co. Ltd. personal communication 2004). Ouslander et al. [11] reported that oxybutynin did not alter intra-ocular pressure in the elderly, indicating that the effects on intra-ocular pressure among patients with no angle-closure glaucoma are minimal. Clinicians should avoid both overestimating drug-induced glaucoma, as this would unnecessarily restrict therapeutic possibilities, and underestimating drug-induced glaucoma, as in the worse cases this can lead blindness (although this outcome is rare). It is necessary to explain symptoms of glaucoma to patients, such as severe eye pain, headache, ‘red-eye’ and visual loss. Blurred vision is usually related to relaxation of the ciliary muscle and temporary impairment of visual accommodation, rather than to elevated intra-ocular pressure. When the diagnosis is uncertain, ophthalmologists should be consulted.

In conclusion, anticholinergics present a risk of precipitating angle-closure glaucoma, but are not contraindicated in the more common open-angle glaucoma or in angle-closure glaucoma that has previously been treated by laser iridotomy. Not all urologists are aware of this difference; some avoid anticholinergics in all patients with glaucoma, and others pay little attention to glaucoma. By routine history taking and referral to ophthalmologists, many patients with OAB and glaucoma can safely benefit from anticholinergics. It would be preferable if the information provided with packages of anticholinergics did not use the general term ‘glaucoma’ as a contraindication, but instead warned patients to seek early medical advice should they develop a painful red eye and visual loss.

ACKNOWLEDGEMENTS

The authors thank Dr Hideki Watanabe and Dr Tomohiro Taki from the Tokai Society of Voiding Dysfunction for allowing them to carry out the questionnaire.

CONFLICT OF INTEREST

None declared.

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Correspondence: Kumiko Kato, Department of Urology, Japanese Red Cross Nagoya First Hospital, Nagoya, Japan.
E-mail: kumi.kato@nifty.com

Abbreviations: OAB, overactive bladder.
Efficacy of extended-release doxazosin and doxazosin standard in patients with concomitant benign prostatic hyperplasia and sexual dysfunction

ROGER S. KIRBY, MICHAEL P. O’LEARY* and CULLEY CARSON†
St. George’s Hospital, London, UK, *Harvard Medical School, Boston, MA, and †University of North Carolina, NC, USA
Accepted for publication 17 October 2004

OBJECTIVE
To report a comprehensive retrospective analysis of the favourable effects of doxazosin extended-release (XL) and doxazosin standard on the sexual health of patients with comorbid benign prostatic hyperplasia (BPH) and erectile dysfunction (ED), augmenting a previous study of 680 patients with symptomatic BPH.

PATIENTS AND METHODS
Men with BPH and aged 50–80 years participated in a randomized, double-blind, double-dummy, parallel-group, multicentre trial, completing a 2-week, single-blind, placebo run-in period before receiving doxazosin XL 4 or 8 mg once daily or doxazosin standard 1–8 mg once daily for 13 weeks. Baseline sexual function and changes from baseline after treatment with doxazosin were evaluated from responses of the International Index of Erectile Function (IIEF) questionnaire (with dysfunction defined as a score of ≤3 for any question) and the five domains for erectile function (intercourse satisfaction, orgasmic function, sexual desire and overall sexual satisfaction).

RESULTS
Of 680 patients randomized into the trial, 237 (35%) had ED at baseline; in these patients there were statistically and clinically significant improvements in each of the five IIEF domains with XL and standard doxazosin (P ≤ 0.0019), with the range of improvement being from 13% to 41%. There were no significant differences between treatment groups. Doxazosin XL consistently improved sexual function, as assessed by the individual questions of the IIEF questionnaire. There was no statistically significant difference between groups for any sexual function question analysed.

CONCLUSION
Doxazosin XL and standard improved sexual function in men with concomitant BPH and ED at baseline. This may represent an action independent of relieving lower urinary tract symptoms, because the beneficial effect of doxazosin was reported in patients with no symptomatic BPH.

KEYWORDS
doxazosin, sexual dysfunction, erectile dysfunction, BPH, extended release
INTRODUCTION

BPH is characterized by BOO that is primarily caused by an enlarged prostate gland and increased smooth muscle tone in the bladder neck [1]. The LUTS that result from BPH and BOO can be stratified as voiding or storage symptoms. It is the degree of the bothersomeness of the overall symptom complex and the degree to which this has compromises the patient’s quality of life (QoL) that most often are the impetus for patients with BPH to seek treatment [2]. Bothersome symptoms, which include urgency, frequency and nocturia, contribute to lack of sleep, anxiety and worry, reduced mobility, interference with leisure activities, compromised sense of well-being, lack of energy/fatigue and negative general perceptions of health.

BPH is the most prevalent benign urological condition, with the risk and severity of symptoms increasing as men age. Based on autopsy data, the prevalence of BPH increases from 30–50% in men aged 60 years to >90% in men aged 80 years [3]. As men age, sexual dysfunction and/or erectile dysfunction (ED) can occur, and is exacerbated by age, cigarette smoking, diabetes, hypertension and its associated treatments, depression, antidepressant therapy, and excessive consumption of alcohol [4]. Likewise, there is a greater risk of ED with an increased incidence of LUTS that is independent of age [5,6].

The relative risk of ED in patients with LUTS is 1.8–7.5 [7]. Worsening QoL measures, including general health status, sexual satisfaction and sexual drive, correlate strongly with increasing severity of LUTS [8]. In addition, sexual activity, including intercourse, is negatively correlated with the severity of LUTS [5]. In a community sample in the UK the age-adjusted rates of sexual dysfunction in men with BPH were 53% for reduced rigidity of erections, 47% for reduced ejaculation and 5% for pain on ejaculation [9]. Another study of men referred to a prostate-assessment clinic for LUTS reported that scores for erections were low in 56% of patients and that 46% of these men satisfied the National Institutes of Health criterion of impotence (not having erections adequate for sexual intercourse) [10]. In a study investigating the importance of sexual life and activity for patients with BPH, sexual intercourse ratings in terms of frequency, quality, ability and partner’s pleasure were listed as important factors in measuring QoL in men with symptoms of BPH [11]. The findings emphasized the importance of sexuality in maintaining a good QoL.

Although standard medical therapy for symptomatic BPH includes surgical intervention and pharmacological treatment, patients and physicians often initially choose pharmacological therapy over surgery because it is less aggressive and more easily reversed, and causes less morbidity and mortality [12]. Pharmacological intervention includes androgen-suppressing 5α-reductase inhibitors, e.g. finasteride and dutasteride, and selective α1-adrenoceptor antagonists, e.g. doxazosin, alfuzosin, prazosin, terazosin and tamsulosin [13]. For symptomatic BPH, doxazosin provides rapid relief and sustained symptom control without the clinically significant adverse events associated with surgery, and the long latency period associated with androgen-suppressing therapy.

Clinical trials with extended-release doxazosin (XL), which was formulated with the gastrointestinal therapeutic system in men with BPH, showed that the XL formulation is as effective as the standard [S] formulation while eliminating the need for forced dose-titration at subtherapeutic doses [14,15]. In that trial comparing the efficacy of doxazosin-S and XL in patients with BPH, after 13 weeks of treatment with XL there were significant favourable treatment effects among all patients in the erectile function domain of the International Index of Erectile Function (IIEF) questionnaire (P = 0.005), independent of the sexual dysfunction status at baseline [16]. The purpose of the present analysis was to more comprehensively evaluate the positive effects of doxazosin-XL and -S on the sexual health of patients with BPH and comorbid ED.

PATIENTS AND METHODS

The methods to determine the efficacy and safety of doxazosin-XL and -S were previously described in a pivotal trial [16] and the combined analysis of that trial data and a placebo-controlled trial of doxazosin-XL and -S [14]. Briefly, this randomized, double-blind, double-dummy, parallel-group, multicentre trial compared doxazosin-XL 4 or 8 mg once daily and doxazosin-S 1–8 mg once daily in men with BPH and aged 50–80 years. After a 2-week screening/washout period (phase I) for individuals requiring tapering from vesico-urethral medication, patients meeting the study inclusion criteria entered a 2-week, single-blind, placebo-run-in period (phase II).

Patients eligible for randomization, based on qualifying urinary flow rates, IPSS and good compliance, were then enrolled in a 13-week double-blind treatment period (phase III). The first study visit was at the end of phase I; visits 2 and 3 were at the end of each week in phase II; and visits 4–6 at 3, 7 and 13 weeks, respectively, in phase III. The study was conducted at 69 centres in Europe, Canada and the Republic of South Africa.

Patients completed the IIEF questionnaire [17] at baseline and the end of the study. Patients who reported that they were sexually active completed a series of 15 questions that characterized five major domains of sexual function, i.e. erectile function, intercourse satisfaction, orgasmic function, sexual desire and overall sexual satisfaction. The total score for erectile function is calculated from Q1–Q5 and Q15, that for intercourse satisfaction from Q6–Q8, that for orgasmic function from Q9 and Q10, that for sexual desire from Q11 and Q12 and that for overall sexual satisfaction from Q13 and Q14 of the IIEF.

Responses to the questions were recorded on a five-point, ordered categorical scale; for 10 of the questions an additional category of ‘not applicable’ was offered as a potential response. Effects of therapy on sexual function were assessed for the subpopulation of men with sexual dysfunction at baseline (defined as a score of 1, 2 or 3 for each of the individual IIEF questions, or a mean score of ≤3 for each question in a domain).

Specifically, the five domains and the responses to Q1 (able to achieve erection), Q2 (erections hard enough for penetration), Q4 (maintain erection after penetration) and Q7 (satisfaction of sexual intercourse) of the sexual function questionnaire from baseline to the end of the trial in patients with sexual dysfunction at baseline were examined. Questions 1, 2, 4 and 7 were analysed because they were considered most relevant to the study.

Adverse events and objective test findings, including electrocardiograph changes and laboratory abnormalities that resulted in a change of study drug dose, were recorded.
Table 1: Patients with sexual dysfunction at baseline

<table>
<thead>
<tr>
<th>Variable</th>
<th>Doxazosin, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIT population analysable for sexual function</td>
<td>-XL</td>
</tr>
<tr>
<td>Patients with baseline IIEF question score ≤ 3</td>
<td>335</td>
</tr>
<tr>
<td>Q1 Able to get an erection</td>
<td>56 (16.7)</td>
</tr>
<tr>
<td>Q2 Erections hard enough</td>
<td>56 (16.7)</td>
</tr>
<tr>
<td>Q3 Able to penetrate</td>
<td>38 (11.4)</td>
</tr>
<tr>
<td>Q4 Able to maintain erection</td>
<td>55 (16.4)</td>
</tr>
<tr>
<td>Q5 Maintain erection to completion</td>
<td>37 (11.0)</td>
</tr>
<tr>
<td>Q6 Attempted sexual intercourse</td>
<td>156 (46.6)</td>
</tr>
<tr>
<td>Q7 Satisfaction of sexual intercourse</td>
<td>37 (11.0)</td>
</tr>
<tr>
<td>Q8 Enjoyment of sexual intercourse</td>
<td>86 (25.7)</td>
</tr>
<tr>
<td>Q9 Frequency of ejaculation</td>
<td>33 (9.9)</td>
</tr>
<tr>
<td>Q10 Frequency of orgasm</td>
<td>51 (15.2)</td>
</tr>
<tr>
<td>Q11 Frequency of sexual desire</td>
<td>109 (32.5)</td>
</tr>
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<tr>
<td>Q14 Satisfaction with sexual relationship</td>
<td>79 (23.6)</td>
</tr>
<tr>
<td>Q15 Confidence to get and keep erection</td>
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</tr>
</tbody>
</table>

RESULTS

Of the 680 men randomized to treatment, 350 were designated to receive doxazosin-XL and 330 to receive doxazosin-S. Table 1 shows the number of patients with sexual dysfunction at baseline in the intent-to-treat (ITT) population, based on sexual function questionnaire scores (individual question scores ≤ 3). Of the 350 patients randomized to the doxazosin-XL, 311 (88.9%) completed the study and 39 (11.1%) discontinued. Of the 330 patients randomized to the doxazosin-S group, 299 (90.6%) completed the study and 31 (9.4%) discontinued, as originally described [16]. Treatment-emergent adverse events were associated with the primary reason for discontinuation in 21 (6.0%) patients on doxazosin XL and 16 (4.8%) on doxazosin-S. Other reasons for discontinuation (≤1.4% of patients) included insufficient clinical response, laboratory abnormalities, death (in one patient taking doxazosin-S, and unrelated to treatment), protocol violations or failure to meet entrance criteria, loss to follow-up, withdrawal of consent, or other miscellaneous causes.

Figure 1 shows the change from baseline in all ITT patients who answered the IIEF questionnaire and were ‘currently sexually active’ at baseline. In these patients, doxazosin-XL consistently improved sexual function regardless of baseline function. The improvement was statistically significant for the intercourse satisfaction and sexual satisfaction domains. Patients receiving doxazosin-XL had a significantly greater increase from baseline (improvement) than those receiving doxazosin-S in the erectile function domain only.

Figure 2 shows the change from baseline to final visit in sexual dysfunction for patients with BPH and receiving doxazosin-XL and -S who had concomitant sexual dysfunction at baseline. There were statistically and clinically significant improvements with both formulations in each of the five IIEF domains (erectile function, orgasmic function, sexual desire, intercourse satisfaction and overall sexual satisfaction, P ≤ 0.0019). There were no significant differences between treatment groups.

**TABLE 1 Patients with sexual dysfunction at baseline**

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Results

FIG. 1. The least squares mean (SEM) change in sexual function from baseline to the end of the trial for all patients with BPH who completed the IIEF questionnaire and were sexually active at baseline. Doxazosin-XL, green; doxazosin-S, red. *P ≤ 0.02 vs baseline.
Figure 3 shows the changes from baseline to final visit for the individual questions of the sexual function questionnaire for patients in the ITT population with sexual dysfunction at baseline. There was no statistically significant difference between the doxazosin treatment groups for any sexual function question.

DISCUSSION

In a previous report from this trial, doxazosin-XL 4 or 8 mg once daily produced significant reductions in BPH symptoms and improvements in maximum urinary flow rates, comparable to that achieved with doxazosin-S 1–8 mg but with earlier onset and enhanced tolerability [16]. We report here that treatment with -XL and -S doxazosin produced significant improvements in all five domains of the IIEF in patients with BPH and sexual dysfunction at baseline. We showed that both formulations of doxazosin improved sexual function in individuals with sexual dysfunction at baseline.

Consistent with our findings, other studies with doxazosin have suggested a beneficial effect on sexual function. In the Prospective European Doxazosin and Combination Trial, abnormal ejaculation was reported in 0.4% of patients receiving doxazosin vs 2.3% and 2.4%, respectively, for patients receiving finasteride or combined therapy with doxazosin and finasteride [18]. Based on IIEF results (in 814 men) it was concluded that there was a correlation between the IPSS and frequency of some sexual problems (completing the sex act, \( r = 0.17, P = 0.0098 \); deriving satisfaction, \( r = 0.14, P = 0.03 \)) but not between sexual dysfunction and maximum urinary flow rate.

In another multicentre study of 102 patients with BPH, the effects of doxazosin treatment on sexual function were evaluated after 3 months [19]; 80 patients with sexual dysfunction were stratified using IIEF scores into three subgroups according to their degree of ED (severe, moderate or mild). After 1 month of therapy with doxazosin there was a significant improvement from baseline in IPSS (\( P < 0.001 \)) and IIEF (\( P = 0.0177 \)) that was more evident in the groups entering the study with severe and moderate ED. The effect was sustained for the 3-month duration of the study and suggested that doxazosin significantly improved voiding symptoms (reduced IPSS) and improved sexual function (reduced IIEF) in patients with BPH.

The Medical Therapy for Prostatic Symptoms trial is the largest long-term study to date in patients with BPH [20]; it compared doxazosin, finasteride and their combination on symptoms and disease progression over a 4-year period in 3047 men. Although both agents alone and combined therapy were associated with a long-term improvement in BPH symptoms and a delay in disease progression, finasteride monotherapy and combined therapy were associated with greater risks of sexual adverse events than placebo (although modest), whereas patients treated with doxazosin monotherapy had rates of sexual adverse events that were similar to those with placebo.

Importantly, in the present analysis of the effect of doxazosin on sexual function in the total population with BPH (Fig. 1) the magnitude of the effect of doxazosin was more modest than in the cohort with comorbid ED (Fig. 2). This finding might be expected for an agent that had a beneficial effect in patients with ED, but had little effect on patients without ED, resulting in a ‘dilution’ of the clinical effect. In addition, although the degree of improvement in sexual function produced by doxazosin may not be equivalent to that produced by agents indicated specifically for ED, in the present patients with BPH, treatment with -XL and -S doxazosin resulted in clinically and statistically significant improvements in ED.

The favourable effects of doxazosin on sexual function were reported in patients who failed to respond to agents indicated for treating ED. For example, in men with ED for whom intracavernosal therapy with alprostadil, a synthetic prostaglandin E1, had failed, doxazosin was added to the treatment regimen to determine the effect of \( \alpha_1 \)-adrenoceptor blockade. After adding doxazosin the mean (SD) IIEF scores were significantly better than at baseline, reaching 48.6 (13.4), 46.4 (10.9) and 51.5 (14.3) at 4, 8 and 12 weeks, respectively (\( P < 0.01 \)). The mean scores for the erectile function and intercourse satisfaction domains were significantly greater with combined therapy (\( P < 0.01 \) and \( P < 0.001 \), respectively). Overall 22 (58%) of the 38 patients in the trial with the combined regimen had a significant therapeutic response (>60% improvement in IIEF score) [21]. These data provide further support for the concept that doxazosin therapy can improve sexual function in patients with pre-existing sexual dysfunction.

A recent trial enrolled 28 patients in a randomized trial to investigate the efficacy and safety of sildenafil combined with doxazosin for treating ED of other than organic causes in patients unresponsive to 3 months of sildenafil monotherapy. Fourteen patients were treated with doxazosin (4 mg daily) and sildenafil (100 mg, 1 h before sexual intercourse); the other 14 received...
sildenafil and placebo. The results were assessed using the IIEF questionnaire before beginning the study, and after 30 and 60 days of therapy. Of the 14 patients treated with doxazosin and sildenafil, 11 had a statistically significant increase in IIEF; in the placebo group, only one man recorded a significant IIEF increase ($P = 0.0016$, between-group difference). Blood pressure showed no significant changes [22].

A large-scale, multinational survey was conducted in the USA and six European countries to systematically investigate the relationship between LUTS and sexual dysfunction in older men [5]. Detailed questionnaires were mailed to a nationally representative sample of men aged 60–80 years in each country. The survey found that sexual disorders and their bothersomeness were strongly related to both age and the severity of LUTS. The relationship between sexual problems and LUTS was independent of comorbidities such as age, diabetes, hypertension, cardiac disease and hypercholesterolaemia. The results highlight the clinical importance of evaluating LUTS in patients with sexual dysfunction, and the need to consider sexual issues in the choice of treatment for managing patients with BPH.

Although TURP is currently considered to be the most effective treatment for BPH, patients often worry about the possibility of worsening sexual function resulting from prostate surgery. The risk of ED after TURP is reportedly 3–35% [23]; although this risk may be related to the incidence of perioperative trauma (capsular perforation at the time of surgery, neurovascular damage, etc.) [24], one study, by The Veterans Affairs Cooperative Study Group, reported that the risk of ED associated with watchful waiting was similar to that with TURP [25].

In a placebo-controlled, comparative study of finasteride in >2300 men with BPH, the incidence of drug-related sexual adverse events, including decreased libido (2.9% vs 1.0%) was significantly higher for patients in the finasteride than in the placebo group ($P \leq 0.01$) [26], ejaculatory disorder (2.1% vs 0.5%) and ED (5.6% vs 2.2%).

In human corpus cavernosum tissue, as in other tissues, sympathetic activity is predominantly mediated through activation of $\alpha_1$-adrenoceptors (for review see [27]). It was suggested that selective $\alpha_1$-adrenoceptor antagonists decrease sympathetic tone in the penis, thereby permitting the nitric oxide-induced relaxation of corporal smooth muscle required for a normal erectile response [28]. However, not all $\alpha_1$-adrenoceptor antagonists are equivalent; tamsulosin, a selective $\alpha_1$-adrenoceptor antagonist that is beneficial in BPH, is associated with ejaculatory dysfunction that may be a result of its action on non-adrenoceptors, e.g. those for dopamine or serotonin ($5-HT_{1A}$) [29,30]. Lepor [31] reported the incidence of abnormal ejaculation with tamsulosin to be as high as 26% at 0.8 mg and 10% at 0.4 mg in patients with BPH, compared with none in patients receiving placebo.

In men aged 40-70 years and with concomitant disease, the prevalence of complete ED has been estimated to range from 9.6% in the entire population to 39% in treated patients with heart disease, 29% in those with diabetes, and 15% in hypertensive patients [4]. In the Treatment of Mild Hypertension Study [32], the prevalence of sexual problems was examined in a population of hypertensive men treated with doxazosin, diuretics, $\beta$-blockers, angiotensin-converting enzyme inhibitors, calcium-channel blockers and placebo. At initial screening, sexual problems were reported by 14.4% of men, with erection problems increasing substantially after 60 years old. In that study, doxazosin was associated with the lowest incidence of erectile problems among all classes of antihypertensives included in the study. All patients randomized to treatment with doxazosin who reported ED at the start of the study returned to normal potency during...
the course of the study, whereas only half of those in the placebo group improved [32].

In conclusion, in patients with BPH and sexual dysfunction at baseline, treatment with doxazosin-XL or -S resulted in a significant improvement in all five sexual function domains of the IIEF. Because the beneficial effect on ED was also reported in patients with no symptomatic BPH, this may represent an action independent of relief of LUTS. However, taken together with the high incidence of comorbid ED in patients with BPH, the beneficial effects of doxazosin on sexual function make doxazosin-XL a particularly appropriate drug to treat most patients with BPH.

ACKNOWLEDGEMENTS

This study was supported by Pfizer Inc and Andrx Laboratories Inc.

CONFLICT OF INTEREST

Roger Kirby was a study investigator and paid consultant for Pfizer until 2002. Source of funding: Pfizer Inc.

REFERENCES

EDITORIAL COMMENT

This elegant and comprehensive analysis by Prof. Kirby gives considerable insight into the impact of α-adrenoceptor antagonists (α-blockers) on the sexual function of patients with BPH. Although this is a retrospective analysis, the sample size and use of validated instruments, e.g. the IPSS and IIEF, is more than sufficient to justify the conclusions. So what can be concluded? For the ≈30% of patients with BPH and comorbid ED there was a clinically significant improvement in sexual function when treated with doxazosin XL. Not surprisingly, when the effect of the drug was assessed across all those with BPH it was more modest; the analogy would be the relative effects of sildenafil in patients with ED and in a study population including patients with ED and ‘normal men’.

Although not absolutely conclusive, there is evidence from the study that the improvement in erectile function was not secondary to the improvement in LUTS. It would certainly be of interest to examine this apparent dissociation in more detail. Overall, this could have considerable impact on the way patients with BPH are managed. There is considerable comorbid sexual dysfunction in this group and increasingly physicians are being warned about potential interactions between α-blockers and phosphodiesterase inhibitors. Potentially, in certain patients with BPH, α-blockers alone could be used to manage both LUTS and comorbid ED. The issue not addressed in this study is whether this is a ‘class effect’ or an attribute of doxazosin alone. Certainly, the gauntlet has been thrown down by the manufacturers of doxazosin XL to those involved with alfuzosin and tamsulosin to ‘step up to the plate’.

MICHAEL WYLLIE, Urodoc, UK
Vardenafil is effective and well-tolerated for treating erectile dysfunction in a broad population of men, irrespective of age

FRANÇOIS GIULIANO1, CRAIG DONATUCCI2, FRANCESCO MONTORSI3, STEPHEN AUERBACH4, GARY KARLIN5, CHRISTIANE NORENBERG6, MARTIN HOMERING6, THOMAS SEGERSON7 and IAN EARDLEY8, for the Vardenafil Study Group

1 Department of Urology, CHU de Bicêtre, AP-HP, Le Kremlin Bicêtre, France, 2 Duke University Medical Center, Durham, North Carolina, 3 Department of Urology, Università Vita Salute San Raffaele, Milan, Italy, 4 California Professional Research, Newport Beach, CA, USA 5 Lawrenceville Urology, Lawrenceville, NJ, USA 6 Bayer Healthcare AG, Wuppertal, Germany, 7 Bayer Inc, Toronto, Ontario, Canada, 8 Pyrah Department of Urology, St. James University Hospital, Leeds, UK, and 9 Acknowledgements

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OBJECTIVES

To assess the efficacy and safety of vardenafil in the treatment of erectile dysfunction (ED) in men of different age groups.

PATIENTS AND METHODS

In a retrospective pooled subgroup analysis of randomized, double-blind, placebo-controlled studies, men from the general population with ED received either placebo or vardenafil 5, 10 or 20 mg over 12 weeks. Efficacy variables included the erectile function (EF) domain score from the International Index of Erectile Function, diary response rates to questions on vaginal penetration and maintenance of erection, and positive responses to the Global Assessment Question (GAQ) ‘Has the treatment you have been taking over the past 4 weeks improved your erections?’ The 1385 men were grouped by age (<45, 45–64 and ≥65 years).

RESULTS

At 12 weeks the EF domain scores approached 20 with vardenafil and 14 with placebo in men aged ≥65 years (P < 0.001 vardenafil 5 mg vs placebo, P < 0.001 vardenafil 10 and 20 mg vs placebo). The corresponding scores were 22 and 14 in men aged 45–64 years and up to 24 and 16 in those aged <45 years (P < 0.03 vardenafil 5 mg vs placebo, P < 0.001 vardenafil 10 and 20 mg vs placebo). Vardenafil generated positive GAQ responses in 71%, 76% and 85% of men aged <45, 45–64 and ≥65 years (P ≤ 0.001 vardenafil vs placebo). The corresponding placebo rates were 23%, 25% and 34%. The most common treatment-emergent adverse events were headache, rhinitis, flushing and dyspepsia, which were mild to moderate, transient and unrelated to age.

CONCLUSION

Vardenafil is an effective and generally well-tolerated treatment for ED, irrespective of age.

KEYWORDS

erectile dysfunction, elderly, oral PDE-5 inhibitors, placebo-controlled clinical trial

INTRODUCTION

Erectile dysfunction (ED) is a common condition affecting up to 30 million men of all ages in the USA. Several reports indicate that its prevalence increases with increasing age [1,2], e.g. in the Massachusetts Male Aging Study, a community-based observational study, the prevalence of severe ED increased from 5% to 15% and the prevalence of moderate ED from 17% to 34% between the ages of 40 and 70 years [3]. Similarly, the National Health and Social Life Survey of 1410 men in the USA reported an increase in the prevalence of ED with age. In that survey, 11% of men aged 40–49 years and 18% aged 50–59 years had difficulty achieving or maintaining an erection [4]. Trends were similar in surveys of older men in California [5], Germany [6], the Netherlands [7] and France [2].

The increased risk of developing ED in elderly men may largely be a manifestation of the developmental physiology of ageing, exacerbated by concomitant risk factors that predispose to ED, e.g. cardiovascular disease and diabetes [3]. The Cologne Male Survey reported age-related increases in the prevalence of diabetes in men with ED, from 0% in men aged 30–39 years to 22% in men aged 60–69 years. The prevalence of hypertension with ED also increased with age, from 11.5% in men aged 30–39 years to 33.3% in men aged 60–69 years [6]. It was suggested that both normal ageing and the accumulation age-related risk factors contribute to the increased prevalence of ED in the elderly.

Sexual activity remains important to men as they age, and, in the absence of health issues, many older men continue to be sexually active [8]. Indeed, surveys indicate that more than half of men aged ≥70 years report being sexually active [5,9], and older men are willing to seek treatment with oral agents for ED [5].

Vardenafil, a potent, selective inhibitor of phosphodiesterase-5 (PDE-5), is effective and generally well tolerated for treating ED, both in the general population with ED [10] and in those who are difficult to treat [11,12]. It was suggested that the pharmacokinetics of vardenafil might differ among different age groups. In healthy men aged 18–45 and...
PATIENTS AND METHODS

The present study is a retrospective pooled analysis of the efficacy and safety data of two randomized, double-blind, placebo-controlled trials. One study, conducted at 60 centres in the USA and Canada, included 805 men and lasted for 26 weeks. The second study, conducted at 47 centres in eight European countries, included 845 men and lasted for 12 weeks. For both studies, 12 weeks only were reported for efficacy data, while all 26 weeks of the North American study were included for safety data. Men were randomly assigned to receive placebo or vardenafil 5, 10 or 20 mg in a 1 : 1 : 1 : 1 ratio in both studies. In the European study about a fifth of the men were randomized to a sildenafil comparator arm and are not included in the current analysis. After a 4-week untreated baseline period, men in each study were asked to report any adverse events and vital signs were monitored in all men receiving treatment. The inclusion and exclusion criteria for the USA trial were described previously [10]. Briefly, both studies included men aged ≥18 years who had been diagnosed with ED for ≥6 months and had been in a stable, heterosexual relationship for ≥6 months. All men also had to have made at least four attempts at sexual intercourse on four separate days during the untreated baseline period, with at least half the attempts being unsuccessful. The studies were conducted with Institutional Review Board/Independent Ethics Committee approval and with signed, written, informed consent from all participants. Exclusion criteria included penile anatomical abnormalities, primary hypoactive sexual desire, ED after spinal cord injury, history of radical prostatectomy, uncontrolled diabetes mellitus, particular serious medical illnesses or concomitant medications, abnormal laboratory values (serum creatinine >25 mg/L, total testosterone below the lower limit of detection), unwillingness to cease using other ED therapies, or to make four attempts at intercourse during baseline. Men who were previously unresponsive to sildenafil were excluded from the USA trial only.

Efficacy and Safety Assessments

Three primary efficacy endpoints were assessed in the pivotal trials and in this analysis for the intent-to-treat (ITT) population. The EF domain scores of the International Index of Erectile Function (IIEF) [15] was calculated as the sum of scores from six IIEF questions (numbers 1–5 and 15) at 12 weeks; missing data were accounted for using ‘last observation carried forward’ analysis. The rates of success in vaginal penetration (Sexual Encounter Profile, SEP-2, ‘Were you able to insert your penis into your partner’s vagina?’) and maintenance of erection during intercourse (SEP-3, ‘Did your erection last long enough for you to have successful intercourse?’) were calculated according to the patient’s diary from randomization to 12 weeks. Diary responses were collected after every attempt at intercourse during the untreated baseline phase and after every dose of study medication during the double-blind treatment phase. The percentages of men responding ‘yes’ at 12 weeks to the global assessment question (GAQ), ‘Has the treatment you have been taking over the past 4 weeks improved your erections?’ provided a secondary efficacy endpoint. For the age-related subgroup analyses, data are presented for men in three age groups of <45, 45–64 and ≥65 years.

Adverse events and vital signs were monitored in all men receiving treatment. Men were asked to report any adverse events occurring throughout the course of the studies, and for an additional 7 days after the final dose of study medication. Safety assessments were acquired at 26 weeks for men enrolled in the North American study, while safety assessments were acquired for participants through the 12-week active treatment period in the European study.

Statistical Analyses of Efficacy Data

For EF domain scores and diary response rates (SEP-2 and SEP-3), analysis of covariance, including terms for treatment, age and age-by-treatment interaction while adjusting for baseline and study, was used to compare differences between the least-squares means of vardenafil and placebo treatment groups. Logistic regression analysis, with terms for study, treatment, age and age-by-treatment interaction, was used to compare treatment group differences in a proportion of men with a positive response to the GAQ. Results from analysis of covariance were reported as least-squares means at 12 weeks for each treatment and subgroup. The estimated proportion of men with a positive response to the GAQ is derived from the logistic regression model. For baseline, observed means are shown and all significance tests of treatment differences were two-sided. There were no adjustments to significance levels to account for multiple efficacy variables and subgroups. Although none of the analyses were formally pre-specified, the pooled-data analyses adhered closely to the predefined statistical analysis plans of the individual studies in terms of variables, times and age intervals. The P value from testing the age-by-treatment interaction terms (by analysis of covariance) was used as a description of the modification of overall treatment effect by age.

Results

In the pooled analysis, 342 men receiving placebo and 1058 receiving vardenafil were available for the safety assessment, with 337 and 1048 men, respectively, included in the ITT population for efficacy analysis. All dosage and age groups took about two doses per week during the study.

The baseline demographics, medical history and duration of ED for the men in the pooled population by dose, drawn from the North American and European pivotal clinical trials, were well balanced for demographics, medical history and baseline ED characteristics (Table 1). The frequency distribution for age was comparable across treatment groups. Men aged 45–64 years represented about two-thirds of the pooled population. Men aged ≥65 years were more likely to have hypertension, hyperlipidemia or a history of cardiovascular disease, and were also more likely to have an organic, as opposed to a...
psychogenic or mixed, cause for their ED. Older men were somewhat less likely to have symptoms of depression. Baseline EF domain scores were slightly lower in men aged ≥65 years than in men aged <45 years.

EF domain scores, adjusted for baseline and study differences, at 12 weeks (Fig. 1A) showed better EF with vardenafil treatment than placebo. Overall, there was no indication that treatment effects varied with age (P = 0.2). Vardenafil (10 and 20 mg only) gave significantly better penetration rates (P < 0.001) and successful intercourse (P < 0.001) than placebo, regardless of age (Fig. 18.C). For example, for the three age categories, the placebo group had a 46–58% penetration success rate (SEP-2), compared with 75–82% in the vardenafil 20 mg group. Penetration success rates with the 5 and 10 mg doses were lower but were ≥70%, except for 52% for vardenafil 5 mg in men aged ≥65 years. The smaller response vs placebo with 5 mg vardenafil in elderly men than in men aged <45 and 45–64 years was also reflected by the test for treatment effect modification by age (P = 0.01). The response rates for SEP-3 (erection lasting long enough to have successful intercourse) were also better for all age groups than with placebo. Men aged <65 years had greater SEP-3 response rates (55–72% vardenafil; 28–39% placebo) than did older men. For men aged ≥65 years the success rate for maintenance of erection was 25% with placebo, 36% with vardenafil 5 mg and 54% with both vardenafil 10 and 20 mg. The differences in SEP-3 response rate between vardenafil 5, 10 and 20 mg were statistically significant for men aged ≥65 years. The test of age-by-treatment interaction (P = 0.07) indicated that the magnitude of the treatment effects over placebo might differ by age.

The percentage of men responding ‘yes’ to the GAQ at week 12 (Fig. 1D) was significantly higher with vardenafil than with placebo in all three age groups (P < 0.001). In men aged ≥65 years the percentage reporting improved erections increased with increasing dose of vardenafil (51% at 5, 71% at 20 mg). Only 23% of men in this age range reported an improvement with placebo. With vardenafil 20 mg the proportion of men responding ‘yes’ to the GAQ was similar among age groups (71–76%), compared to 23–34% of positive responses in men treated with placebo. Thus, it appears that this dose of vardenafil was as effective in improving erections in men aged ≥65 years as in younger men. The model-based test for age-by-treatment interaction showed no evidence that the treatment effect is modified by age (P = 0.5).

Table 1: The baseline demographic details and ED characteristics of a pooled population of men with ED from two randomized, placebo-controlled trials

<table>
<thead>
<tr>
<th>Age category, years</th>
<th>N</th>
<th>&lt;45</th>
<th>45–64</th>
<th>≥65</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td></td>
<td>185</td>
<td>906</td>
<td>310</td>
</tr>
<tr>
<td>Age at enrolment, years</td>
<td></td>
<td>37.2</td>
<td>55.4</td>
<td>69.5</td>
</tr>
<tr>
<td>Race (Caucasian, %)</td>
<td></td>
<td>76.1</td>
<td>83.5</td>
<td>92.4</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td></td>
<td>27.3</td>
<td>28.3</td>
<td>27.7</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td></td>
<td>12.4</td>
<td>22.1</td>
<td>19.7</td>
</tr>
<tr>
<td>Cardiovascular disease, %</td>
<td></td>
<td>0</td>
<td>5.7</td>
<td>11.6</td>
</tr>
<tr>
<td>Hyperlipidaemia, %</td>
<td></td>
<td>8.1</td>
<td>22.7</td>
<td>27.1</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td></td>
<td>12.4</td>
<td>32.6</td>
<td>43.2</td>
</tr>
<tr>
<td>Depressive disorders, %</td>
<td></td>
<td>8.1</td>
<td>5.3</td>
<td>4.5</td>
</tr>
<tr>
<td>Smoking, %</td>
<td></td>
<td>35.1</td>
<td>25.4</td>
<td>13.6</td>
</tr>
<tr>
<td>Prior sildenafil use, %</td>
<td></td>
<td>69.7</td>
<td>71.3</td>
<td>75.8</td>
</tr>
<tr>
<td>Time since: first noticed ED, years</td>
<td></td>
<td>5.1</td>
<td>5.6</td>
<td>6.9</td>
</tr>
<tr>
<td>diagnosis, years</td>
<td></td>
<td>3.0</td>
<td>3.3</td>
<td>4.5</td>
</tr>
<tr>
<td>Cause, %</td>
<td></td>
<td>29.2</td>
<td>49.6</td>
<td>62.3</td>
</tr>
<tr>
<td>Organic</td>
<td></td>
<td>36.2</td>
<td>11.8</td>
<td>4.8</td>
</tr>
<tr>
<td>Psychogenic</td>
<td></td>
<td>34.6</td>
<td>38.6</td>
<td>32.9</td>
</tr>
<tr>
<td>Mixed</td>
<td></td>
<td>13.5</td>
<td>13.2</td>
<td>13.4</td>
</tr>
<tr>
<td>Vardenafil 5 mg</td>
<td></td>
<td>13.1</td>
<td>12.8</td>
<td>11.8</td>
</tr>
<tr>
<td>Vardenafil 10 mg</td>
<td></td>
<td>13.2</td>
<td>13.2</td>
<td>12.8</td>
</tr>
<tr>
<td>Vardenafil 20 mg</td>
<td></td>
<td>14.9</td>
<td>12.7</td>
<td>12.4</td>
</tr>
</tbody>
</table>

Table 2: The percentage incidence of treatment-emergent adverse events in the two pooled randomized studies

<table>
<thead>
<tr>
<th>Event</th>
<th>Age group</th>
<th>Placebo</th>
<th>Vardenafil, mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>&lt;45</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>45–64</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>≥65</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>&lt;45</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>45–64</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>≥65</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Flushing</td>
<td>&lt;45</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>45–64</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>≥65</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>&lt;45</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>45–64</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>≥65</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Adverse events shown had a ≥10% incidence in any age/treatment subgroup, and were rounded to the nearest whole percentage. The total numbers of men for the safety analysis were: age <45, 185; 45–64, 906 and ≥65, 310, with similar numbers of men in the four treatment arms.

Vardenafil was as effective in improving erections in men aged ≥65 years as in younger men. The model-based test for age-by-treatment interaction showed no evidence that the treatment effect is modified by age (P = 0.5).

Safety and tolerability of vardenafil

As expected from the mechanism of PDE-5 inhibitors, the most common adverse events reported were headache, rhinitis, flushing and dyspepsia (Table 2); these were dose-related,
The incidence of serious treatment-emergent adverse events overall was 18/342 (5.3%) in the placebo group, 10/350 (2.9%) for vardenafil 5 mg, 11/358 (3.1%) for 10 mg and 13/351 (3.7%) for 20 mg. Rates of serious adverse events were similar in men aged ≥65 years to those in the total study population, where the serious adverse event rates were three of 78 (3.8%) on placebo (one patient each with accidental injury, chest pain, arthritis), three of 78 (3.8%) for vardenafil 5 mg (one patient each with vascular anomaly, arthritis, prostatic disorder, and bladder calculus), four of 89 (4.5%) for vardenafil 10 mg (one patient each with hernia, aortic stenosis, atrial fibrillation, cardiovascular disorder, and syncope) and three of 85 (3.5%) for vardenafil 20 mg (one patient each with hernia, neoplasm, and prostatic carcinoma). Rates of adverse events leading to discontinuation of study medications were also small in both the total study population (seven/342, 2.0%; eight/350, 2.3%; nine/358, 2.5%; and 23/351, 6.6%) for placebo, vardenafil 5, 10 and 20 mg, respectively and men aged ≥65 years (none, three of 78, 3.8%; one of 69, 1.4%; and eight of 85, 9.4%) for placebo, vardenafil 5, 10 and 20 mg, respectively). The incidence of haemodynamic, vital signs or electrocardiogram abnormalities was similar to placebo irrespective of age group.

DISCUSSION

These results from a pooled analysis of two large phase 3 clinical trials in a general population with ED show that vardenafil improved EF irrespective of age. All four efficacy variables showed a decreasing placebo effect with increasing age, indicating that men aged ≥65 years may have ED which is more difficult to treat. In general, men aged >65 years had a slightly lower response to vardenafil than men aged <45 years. The underlying causes of this response are not completely understood, but might reflect underlying comorbid conditions that are more prevalent in older men (Table 1), and the increased severity of these conditions with age. Nevertheless, vardenafil improved EF relative to placebo for all efficacy measures (EF domain scores, response rates to SEP-2 and SEP-3 and the proportion of men with positive responses to the GAQ) in elderly and younger men. Efficacy was generally dose-dependent, with a minimal effect of age on overall efficacy.

In addition to being retrospective, limitations of the present study include that despite adjusting for baseline and study effects, age groups might have differed in other age-related covariates such as comorbid conditions or cause of ED. However, as a result of randomization in each study, the treatment groups were balanced for each age group. In addition, vardenafil is effective and generally well-tolerated irrespective of comorbid conditions [16], cause and severity of ED [17]. A further limitation in this pooled analysis is that sildenafil nonresponders were excluded from one study, while all sildenafil users were included in the second trial. While it might be predicted that this would result in an
enrichment of this population by PDE-5 inhibitor responders, retrospective analyses show that sildenafil-naive subjects have similar or slightly higher responses to vardenafil than previous users of sildenafil [18].

In epidemiological studies the incidence and severity of ED increases with advancing age [19]. This might be a manifestation of the developmental physiology of ageing; in addition to reductions in plasma androgen levels [20] and other endocrine alterations [21], ageing changes penile anatomy and the cellular and molecular processes of EF. These include deposition and remodelling of connective tissue proteins, increased expression of inflammatory cytokines [22–24], apoptosis of cavernosal vascular smooth muscle cells [25], and loss of endothelium-dependent vasodilatation [26–29]. These processes are common with other areas of the vasculature [30], and are exacerbated in the presence of risk factors that predispose to ED, including hypercholesterolaemia, diabetes and hypertension [31–33]. However, despite the underlying pathophysiology, the efficacy of vardenafil in the present analysis was essentially similar irrespective of age. These results suggest that PDE-5 inhibition with vardenafil ameliorates the physiological changes associated with age-related ED.

Over the past 25 years the medical community has recognized the importance of sex in the quality of life of the ageing population [34]. In the absence of health issues, interest and participation in sexual activity has been shown to continue into old age [8,35,36]. For couples seeking to maintain or improve their sexual relationships, the clinical benefits or the demand for PDE-5 inhibitor therapy in older men should not be underestimated. For example, in a community-based survey of 976 older men in California, 10% reported that they had used sildenafil, although over a third reported that they had used it only once or twice. The percentage of users increased steeply with age, with only 1% of men aged <50 years reporting sildenafil use, compared with 27% of men aged 75–79 years [5]. Another study used a marketing research database of 2000–3000 physicians in the USA; men aged 65–74 years accounted for 20% of the sildenafil prescriptions, and men aged 75–84 years accounted for an additional 6% [37]. These results suggest that, despite the general decline of EF with age, older men continue to maintain an interest in seeking reliable therapy for ED.

Vardenafil was generally well-tolerated in all age groups. The most common adverse events (mild to moderate headache, rhinitis, flushing and dyspepsia) are considered to be associated with the PDE-5 inhibitor class. Except for flushing, these adverse events tended to decrease with increasing age. In this study the rates and identity of severe adverse events showed no age or dose predilection. However, since the Cmax of vardenafil, in men without ED is ≈50% higher in men aged >65 years than in men aged <65 years, judicious dosing should be considered [38].

In conclusion, irrespective of age, vardenafil is effective and generally well tolerated for treating ED in a broad range of men, having improved all key indices of EF relative to placebo.

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The EU Vardenafil Study Group: Belgium: Roger De Bruyne (Ziekenhuis Henri Serruyts, Oostende), Georges Declercq (Algemeen Ziekenhuis, Antwerpen), Dirk Vanderscheuren (UZ Gasthuisberg, Leuven), Francis Duyck (Heilig Hart Ziekenhuis), Benny Verheyden (University Hospital, Antwerp), Eric Wespes (Hôpital Civil – Jumet Hôpital, Jumet); Denmark: Thomas Gerstenberg (Kirurgisk Afdeling Urologi, Herlev); Peter Lyngdorf (Klinik for Seksuelle Dysfunktioner, Gentofte); France: François Giuliano (Centre Hospitalier Universitaire Service d’Urologie, Le Kremlin-Bicêtre); Jacques Buvat Cetparp (Lille Centre d’Étude et de Traitement de la Pathologie de l’Appareil Reproducteur et de la Psychosomatique Résidence de l’Hôpital Edouard Herriot, Lyon); Albert Leriche (Hôpital Henry Gabriele, Saint Genis Laval Cedex Hôpital, Saint Genis Laval), Pierre Bondil (Centre Hospitalier, Chambéry), Pierre Costa (Hôpital Gaston Doumergue, Nîmes), Thierry Lebret (Centre Médico-Chirurgical Foch, Suresnes), Emmanuel Blanc (Hôpital Bichat, Paris Groupe Hospitalier Bichat, Paris), Olivier Lan (Clinique Saint Gérard, Capetrans), Robert Porto (Cabinet Médical – Rodocanachi, Marseille).

United Kingdom: Ian Eardley (Leeds General Infirmary, Leeds), Kanaiyial Desai (Walshgee Hospital, Coventry), Wilbert Dinsmore (Royal Victoria Hospital, Belfast), Phillip Kell (Hospital of St John and St Elizabeth, London), Roger Kirby (St. George’s Hospital, London); M Speakman (Taunton and Somerset Hospital, Taunton), David Ralph (Hospital of St John and St Elizabeth, London), Geoffrey Hackett (The Clinic, Lichfield).

Italy: Francesco Montorsi (Ospedale San Raffaele, Milan), Vincenzo Mirono, Francesco Paolo Selvaggi (Urologia/Bari/Selvaggi Ospedale, Bari), Giorgio Carmignani (Clin. Urologica Discat, Genova), Francesco Francesca (Ospedale Santa Chiara, Pisa), Fabrizio Menchini Fabris (Università di Pisa, Pisa), Enrico Pisani (Ospedale Policlinico, Milan), Ugo Lelio Breda (Ospedale Nuov, Bassano del Grappa), Emanuele Belgrano (Ospedale di Cattinara, Trieste), Gaetano Frajesj (Medicina interna/Fatebenefratelli/ Roma/Frajesse, Rome), Arcangelo Pagliarulo (Azienda Ospedaliero Clinico Consorziale, Bari), Vincenzo Mirono (Policlinico Federico II, Napoli), Vincenzo Gentile (Dip. Umberto Bracci Università degli Studi ‘La Sapienza’ Viale del Policlinico, Roma), Vincenzo Bonifacio (Viale Policlinico, Roma).


Poland: Kazimierz Krajka (Akademia Medyczna, Gdański), Andrzej Borkowski (Warsaw School of Medicine, Warsaw).

Sweden: Christer Dahlstrand (Sahlgrenska Urologisektionen, Göteborg), Peter Ekman (Karolinska sjukhuset Urologkliniken, Stockholm), Björn Lundquist (Lund).

The North American Vardenafil Study Group: Randall P. Abele (Edmonton Prostate Centre, Edmonton, Alberta); Gerald L. Andriole (Washington University School of Medicine, St. Louis, MO); Stephen M. Auerbach.
(California Professional Research, Newport Beach, CA); Jack Barkin (Toronto, Ontario); Winston Barzell (Urology Treatment Center, Sarasota, FL); Donald Bergner (Tampa Bay Medical Research, Inc., Clearwater, FL); Richard Casey (Male Health Centers, Oakville, Ontario); Stacy Childs (Wyoming Research Foundation, Cheyenne, WY); Selwyn Cohen (Clinical Research Consultants, Inc., Trumbull, CT); David O. Cook (Piedmont Medical Research Associates Inc., Winston-Salem, NC); Jeffrey Deeths (Nebraska Clinical Research Center, Omaha, NE); Craig F. Donatucci (Duke University Medical Center, Durham, NC); Mostafa M. Elhilali (Royal Victoria Hospital, Montreal, Quebec); Pamela L. Ellsworth (Dartmouth Hitchcock Medical Center, Division of Urology, Lebanon, NH); Howard B. Epstein (University of Florida – Jacksonville, Health Science Center, Jacksonville, FL); Robert A. Feldman (Urology Specialists, PC, CT Clinical Research Center, Waterbury, CT); Louis Fields (Thornhill, Ontario); Roger Fincher (Spokane, WA); William Fitch (Ill Urology Consultants, PA, San Antonio, TX); Jenelle E. Foote (Midtown Urology, Atlanta, GA); Jeffrey Frankel (Seattle, WA); Harold A. Fuselier (Ochsner Foundation Hospital, Ochsner Clinic, Department of Urology, New Orleans, LA); Larry I. Gilderman (University Clinical Research Associates, Inc., Pembroke Pines, FL); Marc Gittelman (South Florida Medical Research, Aventura, FL); Evan Goldfischer (Hudson Valley Urology Center, Poughkeepsie, NY); James E. Gottesman (Seattle Urological Associates, Seattle, WA); Fred Gover (Virginia Mason Medical Center, Department of Urology, Seattle, WA); Michael Greenspan (Hamilton & District Urology Association, Hamilton, Ontario); Wayne J. Hellstrom (Tulane University Medical Center, New Orleans, LA); Charles B. Herring (New Hanover Medical Research Associates, Wilmington, NC); Gary S. Karlin (Lawrenceville Urology, Lawrenceville, NJ); Joel M. Kaufman (Urology Research Options, Aurora, CO); Robert J. Krane (Massachusetts General Hospital, Department of Urology, Boston, MA); John N. Krieger (A Puget Sound Health Care System, Section of Urology, Seattle, WA); Alan Lau (University of Illinois at Chicago, Chicago, IL); William A. Leitner (Urology Centers of Alabama, PC, Birmingham, AL); Joel Lilly (Seattle Urological Associates, Seattle, WA); Jack Lubensky (Radiant Research, Inc., Center for Clinical Research, Austin, TX); Nizamuddin Maruf (MidAtlantic Clinical Research Center, Rockville, MD); Keith Matthews (Uromed, Montreal, Quebec); Kevin T. McVary (North-western Center for Clinical Research, Chicago, IL); Andrew McCullough (New York University Medical Center, Urology Research, New York, NY); Arnold Meiman (Montefiore Medical Center, Department of Urology, Bronx); William B. Monnig (The Urology Group, Cincinnati, OH); Craig Niederberger (University of Illinois at Chicago, Chicago, IL); Harin Padma-Nathan (The Male Clinic, Beverly Hills, CA); Allan B. Patrick (Fredericton, N.B.); Jon Lee Peterson (Health Advance n Touch Research, Houston, TX); Peter J. Pommerville (Victoria, B.C.); V. Gary Price (North Texas Clinical Research, Fort Worth, TX); George Raad (Metrolina Medical Research Associates, Charlotte, NC); Paul R. Sieber (Urological Associates of Lancaster, Lancaster, PA); Alan W. Skolnick (Health Advance Touch Research, Houston, TX); Christopher P. Steidle (North-east Indiana Research, Fort Wayne, IN); Cecile Storrie (MDS Harris, Inc, Dallas, TX); David Talley (Urology San Antonio Research, PA, San Antonio, TX); Joseph J. Tepas (University of Florida – Jacksonville Health Science Center, Jacksonville, FL); Timothy S. Truitt (Health Advance Institute, Melbourne, FL); Luc Valiquette (Hôpital St. Luc, Montreal, Quebec); Alexander Yukasov (Urology Group of Princeton, PA, Princeton, NJ); Mitchell Wiatrak (Midwest Research Specialists, Milwaukee, WI); John Williams (University of Florida, Jacksonville Health Science Center, Jacksonville, FL); Rafael Wurzel (Grove Hill Medical Center, New Britain, CT); Joseph Zadra (Barrie, Ontario).

**CONFLICT OF INTEREST**

Martin Homering and Thomas Segerson are employees of Bayer Healthcare. Ian Eardley is an investigator for Abbott, Bayer/GSK, Lilly-Icos, Pfizer. Source of funding: Bayer Healthcare Pharmaceutical Division.

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Correspondence: François Giuliano, Department of Urology, CHU de Bicêtre, 78 rue du Général Leclerc, 94270 Le Kremlin Bicêtre Cedex, France.

e-mail: giuliano@cyber-sante.org

Abbreviations: ED, erectile dysfunction; ITT, intent-to-treat; EF, erectile function; IIEF, International Index of Erectile Function; SEP-2, -3, Sexual Encounter Profile – vaginal penetration, maintenance of erection; PDE-5, phosphodiesterase-5, GAIQ, global assessment question.
Transurethral resection of the ejaculatory ducts for treating ejaculatory symptoms

CHRISTOPHER W. JOHNSON, JONATHAN B. BINGHAM, ERIK T. GOLUBOFF and HARRY FISCH
Department of Urology, College of Physicians and Surgeons of Columbia University, New York, NY, USA
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OBJECTIVES
To report our experience with transurethral resection of the ejaculatory ducts (TURED) in infertile men with symptomatic ejaculatory duct obstruction (EDO).

PATIENTS AND METHODS
We retrospectively reviewed the operative cases of one urologist from 1995 to 2001, identifying 15 patients with symptomatic EDO who underwent TURED. These men had normal hormone levels and no other known genitourinary dysfunction. Investigations included a history, physical examination, semen analysis, semen culture, and high-resolution transrectal ultrasonography. Responses to focused questions and semen analysis were evaluated after surgery.

RESULTS
Before surgery, all patients complained of a decrease in the volume of their ejaculate, 14 of 15 had a non-projectile ejaculation, nine had a genitourinary infection necessitating antibiotic treatment, and five had pain with orgasm. The mean ejaculate volume and total motile sperm count was 1.1 mL and 8.1 million sperm per ejaculate. After surgery, at a mean follow-up of 2 months, 10 men reported having projectile ejaculation, and eight reported a marked improvement in their sensation of orgasm. Overall, 14 men reported a subjective improvement in their ejaculation. The average postoperative ejaculate volume was 2.3 mL and the total motile sperm count was 38.1 million per ejaculate.

CONCLUSIONS
Men with symptomatic EDO who underwent TURED showed improvements in their ejaculation, sensation of orgasm, semen analysis values and fertility.

KEYWORDS
ejaculatory duct obstruction, transurethral resection of ejaculatory duct, infertility.

INTRODUCTION
Ejaculatory duct obstruction (EDO) is a known cause of male factor infertility, and should be suspected in men with oligozoospermia, azoospermia, or low-volume, non-projectile ejaculation. Men with EDO might develop symptoms of dysuria, haematopspermia, low-volume ejaculates, non-projectile ejaculation, pain on or after ejaculation, perineal or testicular pain, or low back pain [1]. The prevalence of EDO in the population is unknown, but it is estimated that it is the cause of azoospermia in ~5% of patients [2]. EDO is rare and has various causes; possible congenital and acquired causes include: congenital atresia, duct cysts, trauma, infection, inflammation and calculus formation [3,4]. Evidence of this process can be found by semen analysis and high-resolution TRUS. Before the advent of TRUS, EDO could only be confirmed by vasography [5].

The diagnosis of EDO is important for infertile men as it can be corrected by surgery. Transurethral resection of the ejaculatory duct (TURED) is the standard form of therapy, but there is little published information on how the symptoms of EDO respond to therapy. To examine this question, we report our experience with TURED in men presenting with infertility who had ejaculatory symptoms associated with EDO.

PATIENTS AND METHODS
We retrospectively reviewed the operative log of one urologist (H.F.) from 1995 to 2001. Fifteen men were found to have symptomatic EDO, which was identified as the source of their infertility, and these men were subsequently treated with TURED. The preoperative symptoms included non-projectile ejaculation, a decrease in sensation of orgasm, and/or pain with ejaculation. Investigations included a focused history and physical examination, two or more semen analyses, a semen culture (with PCR analysis), and TRUS. On TRUS, each man was evaluated for prostatic calcifications, ejaculatory duct cysts and the diameter of the seminal vesicles. Seminal vesicles were considered dilated when they were ≥12 mm in diameter.

Each man was treated with TURED using a standard resecting loop in the midline of the proximal verumontanum (described in detail by Goluboff et al. [6], Fig. 1). A vasogram or seminal vesiculogram were not taken. Directly after resecting the EDO the prostate was massaged to show improved flow through the resected ejaculatory ducts, confirming successful treatment. The outcome of the operation was evaluated ~2 months after surgery, and included focused questions about the symptoms of EDO, and a semen analysis.

The inclusion criteria for the study required that all men had at least one of the symptoms of EDO, bilaterally palpable vas deferens, normal hormone profiles (testosterone, oestradiol, FSH and LH), no other known genitourinary abnormality, and were treated with TURED.

RESULTS
Before surgery, 14 of 15 men had a non-projectile ejaculation, nine had a genitourinary infection necessitating
treatment with an antibiotic, four had pain with ejaculation, and two had haematospermia. The mean ejaculate volume and total motile sperm count was 1.1 mL and 8.1 million sperm per ejaculate. On TRUS, 12 men had prostatic calcifications, six had dilated seminal vesicles and five had ejaculatory duct cysts. After surgery, at a mean follow-up of 2 months, 14 men reported a subjective improvement in their ejaculation, and resolution of their haematospermia and pain with ejaculation. They also noted a return to projectile ejaculation and an increase in the volume of their ejaculate. Ten men now reported having projectile ejaculation, eight reported a marked improvement in their sensation of orgasm, and two of the four men who complained of pain with ejaculation reported resolution of the pain. No men reported an exacerbation of their symptoms after TURED. The mean ejaculate volume increased to 2.3 mL and the total motile sperm count to 38.1 million per ejaculate. Four of the six men who underwent long-term follow-up reported successful pregnancy without assisted reproduction techniques. There were no complications associated with the procedure.

**DISCUSSION**

EDO is a rare cause of infertility, but it is essential to diagnose it, as it can be easily corrected with a minor cystoscopic procedure. Detecting EDO has become easier and less invasive with the development of high-resolution TRUS, which by itself has been shown to be very effective for identifying possible EDO [7,8]; it can show cysts or calcifications that might cause blockage, and identifies dilated seminal vesicles. In the present study, seminal vesicles were considered to be dilated if they were ≥12 mm in diameter. Several groups have attempted to establish 15 mm as the threshold for significant dilation, but this has not been universally accepted [6,9–11]. After EDO was suspected, these men underwent TURED. At the time of TURED, patency of the ejaculatory ducts was confirmed by a prostatic massage and by identifying expressed seminal fluid from the ejaculatory ducts. Since 1973, TURED has become the standard treatment for EDO [12], as it is associated with a low risk of complications.

Rare complications include rectal injury, external sphincter injury, bladder neck injury with resulting retrograde ejaculation, and the possibility of urine reflux into the ejaculatory ducts [4,13]. In the present series there were no complications, and nor did Pryor and Hendry [3] report any. Turek et al. [2] had complications in 20% of their patients, and Farley and Barnes [12] reported recurrent stricture formation in about half their patients. The complication profiles can vary widely. The only other technique that has been used for treating EDO is balloon dilatation of the EDO, which has met with mixed results and is usually reserved for EDO with extraprostatic obstruction [14].

There are no published reports on the symptomatology of EDO and how men subjectively respond to treatment. We chose to focus on this issue. Fifteen men were included in the study and 14 reported an improvement in their EDO after TURED. There are several points to be drawn from this. It is possible that most cases of EDO result from a partial blockage and not total obstruction. The incidence of bilateral total occlusion of the ejaculatory ducts is <1% in fertile men [12,15], so it is likely that many men with EDO have partial obstruction that might develop into complete EDO [16]. This would allow for a range of presentations of EDO. Although not all men are left infertile from EDO, most are symptomatic. Importantly, the present study evaluated only infertile men, and it is likely that many fertile men have the symptoms of EDO but have not reported them. This could be evaluated in future studies that include fertile men with similar symptoms. While examining this, it would also be necessary to validate the long-term durability of TURED for proximal EDO. It would be useful to use established validated questionnaires to evaluate these patients’ symptoms.

EDO affects more than a man’s fertility. As with any body system, there is often discomfort with any blockage, as a result of stimulation of pressure receptors in the affected lumen, and this is a possible cause in men with EDO that could explain the physical pain reported by some. However, men with symptoms of EDO often also have a psychological component to their problem; they often have non-projectile ejaculations and low-volume ejaculates, which could be very disturbing to them, and which might be perceived as a sexual malfunction and as a threat to their masculinity. Infertility issues aside, the symptoms of EDO can have a major impact on sexual satisfaction and should therefore be addressed.

In conclusion, EDO is a very treatable disease that can be cured with a simple procedure. This is the first study to focus on the symptomatic improvement of men who have TURED for relieving proximal EDO. This therapy has a positive impact not only on fertility, but also on sexual satisfaction. Long-term prospective trials are necessary to validate the durability of this therapy and its effect on the symptoms of EDO. This initial experience suggests that TURED can have potential new applications for infertile and possibly fertile men with symptomatic proximal EDO.

**CONFLICT OF INTEREST**

None declared.

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Correspondence: Harry Fisch, 944 Park Avenue, 1st Floor, New York, NY 10028–0319, USA.
e-mail: harryfisch@aol.com

Abbreviations: TURED, transurethral resection of the ejaculatory ducts; EDO, ejaculatory duct obstruction.
Pedicled pubic phalloplasty in females with gender dysphoria

CARLO BETTOCCHI*, DAVID J. RALPH and JOHN P. PRYOR
Institute of Urology, St. Peter’s Hospital, UCH London, UK and *Cattedra di Urologia, University of Bari, Bari, Italy
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OBJECTIVE

To describe a novel phalloplasty technique and to study the results and complications in female patients with gender dysphoria.

PATIENTS AND METHODS

Between 1989 and 2000, 85 female-to-male transsexual patients had a phalloplasty fashioned from suprapubic abdominal wall flap that was tubed to form the phallus, and which incorporated the neourethra made from a pedicled tube of labial skin. The complete neourethral reconstruction was in one stage in 32 patients and in two in 48; five patients did not wish to have the neourethra fashioned.

RESULTS

The cosmetic appearance of the phallus was considered good in 68% of the patients. The major complications (in 60 patients) were related to the neourethra (75%) with stricture formation (64%) and/or fistulae (55%) predominating. This complication rate was significantly less (P < 0.001) when the neourethra was created in two stages. Once the neourethra was completed, patients were then offered both penile and testicular prostheses. Sexual intercourse was possible with no prosthesis in 16 patients.

CONCLUSIONS

The pubic phalloplasty offers an acceptable neophallus without disfiguring the donor skin site. The main complications stem from creating the neourethra and these may be reduced by a two-stage procedure.

KEYWORDS

phalloplasty, transsexualism, gender dysphoria

INTRODUCTION

A phalloplasty, or the surgical construction of a penis, is one of the most difficult surgical procedures in reconstructing the genital tract. It is indicated in men where the penis is missing for congenital or acquired reasons, or in women with gender dysphoria. There is general agreement [1] that the ideal technique should: be a one-stage procedure; cosmetically acceptable to both patient and partner; permit standing to void through a competent neourethra; permit penetrative vaginal sexual intercourse; have tactile and erogenous sensitivity; and leave minimal scarring in the donor area.

Bogoras [2] was the first to describe a phalloplasty operation in 1936, and although other techniques [3–9] have been described, none of them meet the ideal considerations, and complications are commonplace. In addition, there are few published series with >20 patients [10–14]. The senior author initially favoured the Gilles technique [3] but abandoned it because of the high complication rate, and changed to a clitoral phalloplasty [10]. The clitoral technique was modified to become the pubic phalloplasty at the end of 1988, and this paper describes the experience with this method in 85 patients

PATIENTS AND METHODS

This is a retrospective review of 85 phalloplasty operations performed between 1989 and 2000 in a tertiary referral centre. All patients (mean age 34.4 years, range 19–54) had been diagnosed as having gender dysphoria by a specialist team of psychiatrists, and had been assessed as suitable candidates for surgery. They had been living in the male role for ≥2 years and had been receiving androgen therapy. Most (83) had already had a bilateral mastectomy at a mean (range) age of 27.9 (15–45) years before they presented for their phalloplasty. Twenty-five patients had already had a bilateral oophorectomy and hysterectomy, and the remaining 60 did so during the phalloplasty procedure. Between 1989 and 1992 the pubic phalloplasty was in one stage (37 patients) but in the latter half of the series (1993–2000) the neourethra was constructed in two stages (48 patients). All patients had a long-term surgical follow-up and their notes were reviewed retrospectively by one of the present authors.

OPERATIVE TECHNIQUE

The patients were placed in a modified lithotomy position using Lloyd-Davies leg supports, and after a full pubic and abdominal shave. Prophylactic cefuroxime and metronidazole were given on the induction of general anaesthesia and continued for 48 h after surgery. The phallus was fashioned from a flap of anterior abdominal wall skin, 11 cm wide and 12 cm long, measured from the base of the clitoris (Fig. 1). When possible, the superficial external pudendal vessels were incorporated into the base of the flap pedicle. After mobilizing the flap, any excess subcutaneous tissue was excised to give a better cosmetic appearance and facilitate tubing the phallus. The anterior abdominal wall skin was completely mobilized up to the costal margins, to enable primary closure of the abdominal wall skin and thereby avoid the need to skin graft the donor site. Hysterectomy and oophorectomy, when desired, were through a transabdominal approach using a midline rectus sheath incision (although the vagina was not excised as a routine). The neourethra in the phallus was fashioned by tubing a 3-cm wide strip of skin from the clitoris and labia major (Fig. 2),...
after infiltrating the tissues with local anaesthetic and adrenaline. The glans clitoris was incorporated into the neourethra to maintain erogenous sensation. The flap that had been tubed over an 18 F silicone catheter was laid, using absorbable sutures, into the suprapubic skin flap, which was itself tubed to form the phallus (Fig. 3). The perineal neourethra was constructed similarly from the skin of the opposite labia, and towards the end of the series the suture line was covered with a Martius fat pad in an attempt to lessen the risk of fistula formation (Figs 4 and 5). A suprapubic catheter was inserted to drain the bladder, and this allowed a urethrogram to be taken 3 weeks after surgery to exclude the presence of a urethral urinary leak. Since 1992 the perineal neourethra was not fashioned until the pendulous neourethra was established satisfactorily. After confirming a competent neourethra, patients were then offered penile and/or testicular prostheses. A single malleable prosthesis was inserted during the early part of the series, but since 1997 a single penile prosthesis (Dynaflex, AMS, Minnetonka, MI, USA) was inserted within a Dacron sheath, which was fixed to the pubic periosteum with bone anchors (15–17, to minimize the risk of erosion and dislocation).

RESULTS

In all, 85 patients had a pubic phalloplasty; there were no complications related to the hysterectomy and oophorectomy. In three patients there was complete loss of the phallus after a gangrenous infection, and these patients had a Gilles phalloplasty. The outcome was considered in the 82 remaining men with a phallus; cosmesis was recorded as good, by both patient and surgeon, in 58 (71%). The abdominal scarring from the donor site was acceptable to the patients, even though the umbilicus was situated much lower than normal. Sixteen patients needed a release of dorsal scar tissue, seven requested that the phallus be lengthened, and one had his neoscrotum refashioned.

Minor wound infection was common (35%) after surgery, but always resolved with conservative management. One patient had a necrotic area on the penis as a result of skin scar from a previous Pfannenstiel incision for his hysterectomy. Skin sensation and erogenous sensation in the glans clitoris were well preserved.

Five patients (6%) did not wish to have a neourethra created and there were complications arising from the neourethra in 60 (75%) patients. Stricture formation and urethral fistulae were common in the same patient, and thus there was a move to a two-stage procedure. This was associated with a decrease in both stricture (94% to 44%) and fistula (94% to 29%) rates. In one patient (two-stage procedure) there was necrosis of the neourethra, as shown in Table 1. The incidence of meatal strictures (27%) was similar in the one- and two-stage procedures (31% vs 25%) but the incidence of distal urethral strictures decreased from 59% to 17% in the two-stage procedure. The incidence of perineal urethral
strictures was low (3%) in both groups of patients.

Perineal fistulae occurred in 94% of the one-stage operations and were associated with distal strictures. The incidence of perineal fistulae decreased to 29% by adopting the two-stage procedure, and was reduced further by using the Martius fat pad. One patient had recurrent episodes of cellulitis in the phallus and the neourethra was excised 21 months after the phalloplasty.

The status of the man’s ability to void at the time of follow-up is shown in Table 2; 15 of the 80 patients were still waiting for the completion of the second stage procedure. Satisfactory voiding while standing was possible for 24 men and a further 16 were able to void but had minor difficulties. Ongoing problems were still present in 29 men.

Sixteen patients were able to have penetrative sexual intercourse with no need for a penile prosthesis, but 17 needed one (eight with a malleable and nine with a Dynaflex). The malleable prosthesis had been lost through skin erosion in six men and 12 were still awaiting operation.

Interestingly, only 25 men had requested testicular prostheses; these were only implanted when there was no longer a risk of UTI, the man was free of complications, and cosmetically acceptable.

**DISCUSSION**

It is necessary for all patients with gender dysphoria to be correctly diagnosed by two psychiatrists with a special interest and experience in the field before they start on the long and difficult path of changing their gender. The patients will have been under psychiatric supervision for ≥2 years, and often for as many as 10 years, before referral to the surgical clinic. They usually have some idea of the possibilities for surgery but have unduly high expectations of the outcome, and usually fail to appreciate the risks involved. They are committed to changing their body image and rarely fail to proceed. Many of them had friends who had already undergone surgery at our centre and only sought referral once the friends had completed the procedures.

Complications are common after all phalloplasty surgery and Zielinski [13], using a lateral groin flap in 127 patients with gender dysphoria, reported good results in 96 (76%) with complications occurring in only 20 (16%), and with a complete loss of phallus in five. A neourethra was fashioned in only five patients and most of the complications stem from urinary tract problems. Rohrmann and Jakse [14] reported a 58% incidence of urethral complications in a series of 25 patients having a free radial forearm flap phalloplasty, and Fang et al. [11] had a 41% fistula and 14% stricture rate in 22 patients using a free radial osteocutaneous flap phalloplasty.

Urethral complications were common in the current series and the treatment of meatal stenosis by urethrotomy and/or urethral dilatation served as a temporary measure until definitive surgery by meatoplasty or urethroplasty. The fistula usually formed at the junction of the native and neourethra in the perineum, and was usually secondary to distal urethral stenosis. The incidence of fistula was reduced by using the Martius fat pad inserted between the suture lines, and by switching to the two-stage procedure. Hair formation and the entrapment of concretions were occasionally a problem, and usually treated endoscopically. Every effort should be made to avoid using hair-bearing skin.

The cosmetic outcome using this technique was well accepted by the patients and genital sensation was maintained by the clitoris being incorporated into the neourethra. The surgical scar at the base of the phallus tends to hold it up as a ‘pseudo-suspensory ligament’ and this facilitates vaginal penetration. One patient preferred the phallus to hang downwards and requested a releasing operation. The forearm-flap phalloplasty probably gives a better cosmetic appearance of the phallus, but has the drawback of requiring a large skin graft to the donor site on the forearm. It also has the risk of urethral complications, as has already been described. It is a choice for the patients to make and in this respect it is useful to have a library of photographs for them to study, and better still, an operated patient for them to talk to.

Penetrative sexual intercourse was possible in 16 men, with no penile prosthesis. A penile prosthesis was necessary in others, but almost half the implanted malleable prostheses eroded distally. This problem was overcome using a hydraulic prosthesis implanted within

![Image](69x752 to 593x769)
a Dacron sleeve [15,16]. The scrotal pump of a
two- or three-part hydraulic prosthesis may
act in place of a testicular prosthesis. In the
later part of this series hydraulic prostheses
were used (Fig. 6) as they had proved to be
superior and safer, although there is a risk of
pubic periostitis or osteomyelitis. The
presence of good sensation in the phallus
reduces the risk of cutaneous erosion, as does
the use of a hydraulic device, which will
reduce tissue ischaemia resulting from
persistent pressure over the tissues [17].

Testicular prostheses are relatively easy to
insert and the results, both in terms of
cosmesis and complications, were good.

It is surprising that although nearly every
patient wished to have them inserted
before surgery commenced, very few of
them bothered after they had completed
the rest of the surgery.

There are no validated questionnaires for
surgery in patients with gender dysphoria.
Barrett [18] compared the psychological
status of 23 patients awaiting surgery with 40
who had completed their phalloplasty at our
centre. He found that the group after surgery
were happier with their body image, but had
higher depression ratings and lower
relationship ratings.

In conclusion, there is still no ideal technique
for phalloplasty, but the pubic phalloplasty is
a simple procedure with minimal scarring in
the donor area. It is well accepted by the
patient and his partner, and occasionally rigid
enough for penetrative sexual intercourse
with no need for further surgery. There are
still problems with the neourethra, but the
incidence of complications has been reduced
by using a staged procedure. Implantation of
a hydraulic prosthesis further reduces the
complication rate.

CONFLICT OF INTEREST

None declared.

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Correspondence: Carlo Bettocchi, Cattedra di Urologia – Policlinico, University of Bari, Piazza G. Cesare 11, 70124 Bari, Italy. e-mail: bettocchi@urologia.uniba.it
**Cavernosal dysfunction in a rabbit model of hyperhomocysteinaemia**

ROBERT W.A. JONES*, JAMIE Y. JEREMY*, ANTHONY KOUPPARIS†, RAJ PERSAD† and NILIMA SHUKLA*

*Bristol Heart Institute University of Bristol, and †Department of Urology, Bristol Royal Infirmary, Bristol, UK

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**OBJECTIVE**

To investigate the effect of sustained hyperhomocysteinaemia (HHCy) on cavernosal smooth muscle function in a rabbit model of HHCy; developed using a methionine-enriched diet in which cavernosal responses were characterized, as elevated plasma levels of homocysteine may be a risk factor for vasculogenic erectile dysfunction.

**MATERIALS AND METHODS**

Six New Zealand White rabbits were fed a diet supplemented with methionine (20 g/kg chow) for 4 weeks, while six control animals were fed a standard diet. Cavernosal strips were mounted in an organ bath and relaxation assessed when stimulated with carbachol, sodium nitroprusside (SNP), or noncholinergic, nonadrenergic (NANC)-mediated relaxation to electrical-field stimulation (EFS). Cavernosal tissue cGMP levels were assessed using an enzyme-linked immunosorbent assay, and superoxide (O$_2^-$) production assessed using an assay of the superoxide dismutase (SOD)-inhibitable reduction of ferricytochrome c.

**RESULTS**

The methionine-rich diet led to an early but sustained HHCy; cavernosal strips from animals after 4 weeks of HHCy had a significantly impaired relaxation response to carbachol, an index of endothelium-dependent nitric oxide (NO)-mediated relaxation. This impairment was reversed by incubating with either SOD or catalase. Relaxation with either SNP, an index of endothelium-independent NO-mediated relaxation, or NANC-mediated EFS-induced relaxation, was unaffected by HHCy. There was a corresponding significant reduction in cavernosal cGMP levels (index of NO activity) in the HHCy group, with a more than five-fold increase in cavernosal tissue O$_2^-$ production.

**CONCLUSION**

Supplementing the diet of rabbits with methionine for 4 weeks caused an early and sustained HHCy and promoted a marked inhibitory effect on endothelium-dependent relaxation and NO formation in isolated corpus cavernosum, an effect mediated by reactive oxygen species.

**KEYWORDS**

homocysteine, erectile dysfunction, endothelium-dependent, nitric oxide, superoxide

**INTRODUCTION**

Risk factors for cardiovascular disease (CVD), including diabetes mellitus, dyslipidaemia, hypertension and smoking, are also risk factors for vasculogenic erectile dysfunction (ED) [1–5]. Endothelial dysfunction is a common denominator of these cardiovascular risk factors, and is considered to be pivotal in their association with ED [1–5]. In turn, a reduction of endothelial nitric oxide (NO)-mediated cavernosal relaxation is found in patients with vasculogenic ED [6].

Another risk factor for endothelial dysfunction and CVD is an elevation of the amino acid homocysteine, i.e., hyperhomocysteinaemia (HHCy) [7,8]; this is associated with impaired NO-mediated relaxation in vascular tissues [9,10], and increased plasma homocysteine levels are associated with impaired NO-mediated vasodilatation in human resistance arteries [10]. Animal models of diet-induced HHCy have been established in the rat [11–13] and monkey [14], and are similarly associated with impaired endothelium-dependent vascular smooth muscle relaxation [11–14]. Homocysteine elicits angiopathic effects principally through auto-oxidation, generating reactive oxygen species (ROS) including superoxide (O$_2^-$) and hydrogen peroxide (H$_2$O$_2$) [9,15,16]. O$_2^-$ promotes vasoconstriction and reacts with NO to form peroxynitrite (ONOO$^-$), thereby limiting endothelial NO availability in vascular tissues [17].

It was proposed that HHCy may have an equivalent effect in corpus cavernosal smooth muscle, and that as such HHCy may represent an additional vascular risk factor for vasculogenic ED [5,18]. Support for this hypothesis comes from the finding that homocysteine inhibited acetylcholine-induced relaxation and cGMP production in the rabbit corpus cavernosum, *in vitro* [18].

The inhibitory effect of homocysteine was reversed by either superoxide dismutase (SOD, which inactivates O$_2^-$) or catalase (which inactivates H$_2$O$_2$) [18]. It was therefore proposed that through the inhibitory effect of these ROS on NO bioavailability in the corpus cavernosum, HHCy may be associated with ED [18].

The effect of HHCy on cavernosal function in patients or animals has not been reported. In the present study we first aimed to establish a rabbit model of HHCy, and second to examine the effects of HHCy on cavernosal smooth muscle function, evaluating the potential role of ROS.

**MATERIALS AND METHODS**

New Zealand White rabbits (3 kg initial weight) were fed a standard rabbit chow supplemented with 2% methionine (20 g/kg chow, SDS Ltd, UK). Rabbits were allowed free
access to the chow. Controls consisted of rabbits fed a similar chow but with no methionine supplement (RabM®; SDS); six animals were used in each group. At 1, 2 and then 4 weeks after introducing the diet, blood was collected from the ear vein and plasma prepared. Plasma homocysteine levels were measured using HPLC. Cavernosal function was then assessed 4 weeks after introducing the diet.

Rabbits were killed by an intravenous injection with pentobarbitone (100 mg/kg) given via the lateral ear vein. The penis was harvested and the corpus cavernosal tissue dissected from the tunica albuginea, placed in cold Dulbecco’s modified Eagle medium (DMEM, Gibco BRL Life Technologies Ltd, Paisley, Scotland, UK), and used within 6 h. Strips of cavernosal tissue (8 × 2 mm) were mounted in organ baths for isometric tension studies. The size and weight of the cavernosal strips were identical in both the control and methionine-fed rabbits.

The strips were mounted vertically in 20 mL chambers, equipped with two parallel platinum electrodes, containing Krebs’ Ringer bicarbonate buffer (KRB) maintained at 37 °C by a thermoregulated circuit. Tissues were suspended between tissue bearers, one in a fixed position and the other attached to a force-displacement transducer, and data recorded on a computer. The KRB solution was bubbled with a mixture of 95% air/5% CO₂, maintained at pH 7.4. An initial tension of 2 g was applied to the suspended tissue strips. All strips were equilibrated for 1 h with frequent changes of KRB, after which the tissues were pre-contracted with phenylephrine (100 μmol/L) and then relaxed with cumulative doses of the acetylcholine analogue, carbachol (0.01–100 μmol/L). To investigate the potential effects of O₂⁻ and H₂O₂ on endothelium-dependent cavernosal relaxation in HHCy, the effects of SOD and catalase were assessed. A dose–response curve to carbachol was first obtained; then after three washes with fresh KRB, tissues were incubated for 30 min with either SOD (300 U/mL) or catalase (100 U/mL) and the relaxation with carbachol repeated.

In separate experiments, relaxation was similarly induced using the endothelium-independent vasodilator sodium nitroprusside (SNP, 0.01–100 μmol/L). The relaxation response was expressed as a percentage inhibition of the phenylephrine-induced contraction. Four strips from one animal were used for each dose-response study, with a total of six animals being used for each component of the study.

To assess nonadrenergic, noncholinergic (NANC) nerve-mediated cavernosal relaxation, cavernosal strips from control and methionine-fed rabbits were constructed as above, but in KRB containing 1 μmol/L atropine and 5 μmol/L guanethidine. Tissues were pre-contracted with 100 μmol/L phenylephrine. Electrical-field stimulation (EFS) was applied using a tissue stimulator (Multistim® D330, AD Instruments, Hastings, UK), delivering single square waves (300 mA, duration 0.8 ms) over a range of frequencies that gave an incremental increase in the relaxation response (0.5–20 Hz), in 5-s trains at 2-min intervals. The relaxation response was expressed as the percentage inhibition of phenylephrine-induced contraction.

Cavernosal segments from control and methionine-fed rabbits were placed into polypropylene tubes containing 200 μL KRB with 250 μmol/L isobutylmethylxanthine (a nonspecific phosphodiesterase inhibitor). cGMP formation was then stimulated with 10 μmol/L calcium ionophore (A23187, an activator of endothelial NO synthase). Tubes were incubated for 20 min at 37 °C, and the reaction then terminated by adding 100 μL 1 mol/L perchloric acid, and the tissues sonicated. Supernatants were neutralized with 100 μL of 1 mol/L K₂PO₄. Aliquots were then taken and acetylated with trifluoroacetic anhydride (1:2; v/v) and concentrations of cGMP measured using a cGMP competitive enzyme immunoassay kit (Biotrak™, Amersham Pharmacia Biotech UK Ltd, Bucks, UK). Basal and stimulated cGMP levels from control and methionine-fed rabbit cavernosal segments were compared (six in each group).

The O₂⁻ in cavernosal tissues was measured using a modified method of the cytochrome c-based spectrophotometric assay. Cavernosal segments (2 × 2 mm) from HHCy and control animals (six each) were allowed to equilibrate at 37 °C for 10 min in DMEM (with no phenol red). Cytochrome c (20 μmol/L), with or without CuZnSOD (300 U/mL, final concentration) were added to the segments and incubated at 37 °C in a 95% air/5% CO₂ incubator for 1 h, after which 200 μL of the reaction medium was taken and the reduction of ferricytochrome c measured as the absorbance at 550 nm in a spectrophotometer. The amount of O₂⁻ release was calculated by dividing the difference in absorbance of the samples with and without SOD by the molar extinction coefficient for the change of ferricytochrome c to ferrocyanochrome c (E₂₅₀ 21.1 mmol/L⁻¹·cm⁻¹). The results were expressed as nmol O₂⁻/mg wet weight per hour.

The means of quadruplicate samples from an individual animal were calculated and then the mean of the means of six animals used for data analysis. Data were analysed using ANOVA for multiple comparisons. The two groups were compared using Student’s t-test where the ANOVA indicated significance for multiple comparisons, with statistical significance accepted at P < 0.05.

RESULTS
The diet of 2% methionine led to an early and sustained HHCy (Fig. 1). Plasma levels of homocysteine in the methionine-enriched group were significantly higher at 1 and 2 weeks after introducing the methionine supplement (Fig. 1), and at 1 month were markedly higher than that in controls (mean 214 μmol/L in the HHCy and 16 μmol/L in controls, P < 0.001).

The contractile response to phenylephrine was equivalent in cavernosal strips from control and HHCy animals (data not shown). Carbachol-stimulated relaxation of the corpus cavernosa was significantly impaired in the HHCy than in control tissues (Fig. 2a, P < 0.001). The impaired response to carbachol in cavernosal strips from rabbits with HHCy was reversed by incubating with either SOD (Fig. 2b, P < 0.001) or catalase (Fig. 2c, P < 0.005). SOD and catalase had no significant effect on carbachol-elicited relaxation in cavernosal tissue from control animals (data not shown). This shows impaired endothelium-dependent cavernosal relaxation in HHCy, an effect reversed through inhibition of O₂⁻ and H₂O₂.

In contrast, there was no difference in cavernosal relaxation elicited by SNP between control and HHCy rabbits (Fig. 3a). This
indicates that the methionine-rich diet promotes an inhibitory effect on NO-mediated relaxation at the endothelium, but has no effect on guanylate cyclase activity. NANC-mediated relaxation was similarly unaffected by HHCy after 4 weeks of the 2% methionine diet (Fig. 3b).

Basal levels of cavernosal tissue cGMP did not differ significantly between the HHCy and control animals, with mean (SEM) values (six samples) of 2.13 (0.48) and 1.72 (0.48) fmol/mg tissue per min, respectively. However, when stimulated with A23187, cGMP levels were significantly less (*P < 0.01) in tissues from HHCy rabbits than controls, at 1.95 (0.46) and 4.28 (0.65) fmol/mg/min. This supports a reduction in endothelial NO activity in HHCy cavernosal tissues. There was correspondingly significantly (*P < 0.02) more cavernosal tissue $O_2\cdot$ formation in HHCy than in control rabbits, at 195.7 (39) and 33.6 (26) nmol/mg/h.

**DISCUSSION**

HHCy is a recognized risk factor for endothelial dysfunction and its related disorders, including CVD and thromboembolic disease [7-9]. Homocysteinuria, a rare autosomal recessive genetic disorder (1 in 200 000 births), is associated with severe HHCy and premature death from myocardial infarction, stroke or pulmonary embolism [7]. Moderate HHCy is commonly caused by genetic factors or B vitamin deficiencies (especially folate, B6 and B12) [19]. Prospective studies have indicated that individuals with a plasma homocysteine in the top quartile of the population (>12 μmol/L) have twice the risk of CVD [19]. A recent meta-analysis of clinical studies indicated a causal relationship between moderate HHCy and CVD [8].

The vasculopathic effect of HHCy appears to be mediated through the induction of endothelial dysfunction, which is associated with a reduction in NO-mediated relaxation in vascular tissues [10,20]. As such, HHCy has been cited as a possible risk factor for vasculogenic ED [18], although to date no clinical studies have explored this potential association. The present study shows that a 2% methionine diet fed to rabbits for 4 weeks induces HHCy and an inhibitory effect on carbachol-stimulated relaxation of the rabbit corpus cavernosum, indicating an effect on endothelial NO-dependent relaxation. cGMP formation in response to the calcium ionophore A23187, which activates endothelial NO synthase through elevation of cytosolic Ca$^{2+}$ [21], was also reduced. In contrast, relaxation of the corpus cavernosum in response to SNP, which activates guanylate cyclase directly [21], effectively bypassing the NO synthase, was unaffected by HHCy. As NO activates guanylate cyclase, which in turn elicits relaxation of cavernosal smooth muscle by activating protein kinase G and suppressing Ca$^{2+}$ mobilization [21], we conclude that HHCy promotes an impairment of cavernosal relaxation through a reduction of endothelial NO bioavailability and not a reduction of guanylate cyclase activity.

HHCy also had no effect on relaxation of the corpus cavernosum when elicited with EFS, which promotes relaxation of the corpus cavernosum by activating NANC fibres, which release dilator peptides and NO [22]. These data therefore indicate that HHCy has no...
Impaired endothelium-dependent cavernosal relaxation in rabbits with HHCy was reversed in this study by SOD (which converts O$_2^-$ to H$_2$O$_2$) or catalase (which converts H$_2$O$_2$ to H$_2$O), indicating a pathological role for these ROS. However, the lesser response obtained with catalase indicates that O$_2^-$ is the major determinant of the present effects. This corresponds to similar protective effects of SOD and catalase on the impairment of cavernosal relaxation by homocysteine, in vitro [18]. In addition, the present model of HHCy was associated with significantly increased cavernosal O$_2^-$ formation. O$_2^-$ has been implicated in the pathophysiology of both CVD and ED through its reaction with NO, forming ONOO$^-$ as a product [2,5]. Apart from reducing NO availability, the production of ONOO$^-$ is itself vasculopathic, as it reacts readily with tyrosine residues, thereby disrupting protein function. An imbalance between NO and O$_2^-$ levels, resulting in a condition of 'oxidant stress', is considered axiomatic in the development of endothelial cell dysfunction in atherogenesis [26] and may have an equivalent significance for vasculogenic ED [2,5]. Therefore we conclude that HHCy impairs cavernosal relaxation through the negation of NO bioavailability, an effect mediated by the actions of the ROS, O$_2^-$ and H$_2$O$_2$.

HHCy has been induced in both humans [9,27] and a variety of animal models [11–14,28,29] through ingestion of methionine, the metabolic precursor for homocysteine. Methionine is the sole dietary source of homocysteine, and forms homocysteine in the liver through the donation of a methyl group, via the trans-methylation pathway [19,30]. In a model of chronic HHCy in the rat, giving a 2% methionine diet for 2 years lead to arterial wall morphological changes associated with atherogenesis and premature ageing [11]. However, impairment of endothelium-dependent arteriolar relaxation was apparent after only 4 weeks in rats given methionine (1 g/kg body weight) in their drinking water [12]. In monkeys fed a 1% methionine diet for 4 weeks there was a slight increase in plasma homocysteine, with significant impairment of endothelium-dependent vascular relaxation [14].

Experience with methionine diet-induced HHCy in the rabbit is more limited. Rabbits fed a 3% D,L-methionine diet for 22 weeks developed HHCy and progressive atherosclerosis [28]. Rabbits fed a 1% methionine diet for 12 weeks developed HHCy and early features of atherosclerosis [29]. The minimum daily sulphur amino acid (methionine and cystine) requirement for normal growth in New Zealand White rabbits is 6.2 g/kg chow [31]. To provide half of this quota in the form of methionine, standard rabbit chow (e.g. RabMa) contains 3 g/kg D,L-methionine by weight (0.35%). We hypothesized that a diet supplemented with 2% methionine (i.e. 20 g/kg chow) over a 4-week period would induce HHCy with no overt atherosclerosis, and this was confirmed here. In the present study high concentrations of plasma homocysteine were achieved (200 μmol/L) with this dietary formulation, which would be considered severe HHCy. However, clinically, most patients with HHCy have a mild version of the condition (i.e. >15 μmol/L). Further studies are required to determine whether lower concentrations of methionine would elicit a milder form of HHCy but would still promote ED.

One feature homocysteine is that its effect on NO formation is markedly augmented by copper [15,18], itself an independent risk factor for developing vasculopathy [32]. In isolated rabbit aorta and cavernosum, copper augmented the inhibitory effects of homocysteine on endothelium-dependent relaxation, in vitro [15,18]. Homocysteine has also been shown to have a greater negative effect on endothelial NO in an experimental rabbit model of diabetes mellitus [33], which is itself associated with increased plasma copper [34] and homocysteine levels [35]. These interactive effects were shown to be mediated by an augmentation of O$_2^-$ formation [15,18,33]. Diabetic rabbits have been shown to be susceptible to homocysteine-mediated angiopathy at lower concentrations of homocysteine than non-diabetic animals [33]. It was therefore suggested that the full pathogenic impact of HHCy should be viewed in relation to other risk factors, in particular diabetes and transition metals [33]. Further studies are required to explore these potential interactive effects of these factors on cavernosal function.

To summarize, a diet with 2% methionine for 4 weeks leads to HHCy in rabbits; this was associated with inhibition of endothelium-dependent relaxation and NO-mediated cGMP formation in the isolated corpus cavernosum, an effect mediated by ROS. This study provides further support for the hypothesis that HHCy represents a vascular risk factor for ED by impairing cavernosal endothelial NO synthase activity. Further prospective studies in patients with ED are required to determine whether these observations are of clinical relevance, and in particular whether there is a causal link between homocysteine, diabetes, transition metals and ED.

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35. Jeremy JY, Shukla N, Angelini GD.

Correspondence: Jamie Y. Jeremy, Bristol Heart Institute, Bristol Royal Infirmary, University of Bristol, Bristol BS2 8HW, UK. e-mail: j.y.jeremy@bris.ac.uk

Abbreviations: CVD, cardiovascular disease; ED, erectile dysfunction; NO, nitric oxide; HHCy, hyperhomocysteinaemia; ROS, reactive oxygen species; SOD, superoxide dismutase; DMEM, Dulbecco’s modified Eagle medium; KRB, Krebs’ Ringer bicarbonate buffer; SNP, sodium nitroprusside; NANC, nonadrenergic, noncholinergic; EFS, electrical-field stimulation.
Comparison of laparoscopic and open donor nephrectomy: UK experience

COLIN H. WILSON, AFTAB A. BHATTI, DAVID A. RIX and NAEEM A. SOOMRO
Department of Urology, The Freeman Hospital, Newcastle-upon-Tyne, UK
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OBJECTIVE
To compare our early experience of laparoscopic donor nephrectomy (LDN) with a contemporary cohort of conventional open donor nephrectomy (ODN).

PATIENTS AND METHODS
Transperitoneal left-sided LDN was offered to carefully selected potential live kidney donors on the basis of vascular anatomy. The first 20 donors who underwent LDN were compared with a control group of 20 patients who had ODN. Donors and recipients were compared for demographics, intraoperative variables, postoperative complications and allograft function.

RESULTS
There was no peri-operative mortality in either group. No laparoscopic procedure required open conversion. The operating time was comparable (165 vs 153 min); LDN was associated with significantly less intraoperative blood loss (200 vs 350 mL; Mann–Whitney U, \( P = 0.01 \)) and hospital stay (3 vs 5 days; \( P < 0.001 \)). The graft warm ischaemic time was significantly longer for LDN (5 vs 2 min; \( P < 0.001 \)) but this did not appear to affect either the delayed graft function rate (5% vs 10%, not significant) or serum creatinine level at discharge (125 vs 126 \( \mu \)mol/L).

CONCLUSIONS
UK centres with experience of advanced laparoscopy and ODN can safely offer LDN to potential live donors.

KEYWORDS
laparoscopy, live donor, renal transplantation.

INTRODUCTION
The number of patients on the UK renal transplant waiting list is set to rise, from the current level of \( \approx 4000 \) to \( > 6000 \) by 2010 [1]. For most patients a live donor may be their best hope of transplantation, as the cadaveric donor pool continues to contract. Kidney grafts from live donors survive longer than grafts from cadaveric donors (12 vs 8 years) [2]. Increasing the proportion of live donor-derived grafts may therefore confer the additional benefit of reducing re-transplantation requirements. The major disincentive for relatives and partners contemplating kidney donation is the pain and morbidity associated with open donor nephrectomy (ODN), time off work and the flank scar [3,4].

Laparoscopic DN (LDN) was first reported by Ratner et al. in 1995 [5], and since then a considerable number of USA and European centres have adopted the technique. In 2001 a survey of 31 high-volume USA transplant centres reported only one that was neither currently offering nor planning to offer LDN...
Patients and Methods

Data were gathered prospectively on all live kidney donations taking place in the authors’ institution. All suitable donors were offered and allocated to either left-sided LDN or right-sided ODN. After completing 20 LDN procedures in January 2004, the previous 20 consecutive ODN procedures were subsequently identified as the control group.

The donor and recipient combinations were initially assessed for suitability, in accordance with British Transplant Society guidelines [10], by nephrology teams throughout the region. Potential donor–recipient combinations between unrelated individuals, as defined by the definitions of the Human Organ Tissues Act 1989, were independently scrutinized by the UK Live Transplant Assessment organization.

Evaluation for all surgical procedures was undertaken at the transplant unit. Mandatory preoperative investigations consisted of a donor and recipient risk assessment by a consultant transplant surgeon, anatomical evaluation (MR angiography and contrast-enhanced CT) and a multidisciplinary review; some surgical candidates also required further assessment by specialist medical teams. One consultant reviewed the donors in clinic and offered them either LDN or ODN during the consent process for surgery. The only determinant of the operative technique offered was the renal vascular anatomy, as defined by the radiological investigation. Donors with either a single left renal artery or two arteries bilaterally were offered LDN; donors with complex vascular anatomy on the left side were offered right-sided ODN.

Laparoscopic donors were informed that this was a new procedure, successfully trialled at other centres, but with a risk of conversion to open surgery and uncertain results. All donors were managed on a separate ward from recipients and received multimodal thromboembolic prophylaxis during admission. Both groups of donors received an induction dose of two broad-spectrum antibiotics and were catheterized in the anaesthetic room. The donor nephrectomy and recipient implantation procedures were performed concurrently, with two separate surgical and anaesthetic teams working in adjacent operating theatres. Continuous liaison between the teams aimed at synchronizing the nephrectomy and implantation in an effort to minimize the graft cold–ischaemia time. On the first day after surgery the urinary catheter and wound drain, if present, were removed. Discharge from hospital was overseen by a consultant and considered when wound pain was controlled with oral analgesia, large bowel function had returned and the patient was mobilizing independently.

For ODN, all donors had an epidural catheter placed while in the anaesthetic room. ODN was performed via a loin incision in the conventional manner, and according to the consultant surgeon’s preference. Fluid management before and during ODN were also at the senior operator’s discretion.

The LDN was transtotional, and described extensively in previous reports [5,11]. The first LDN in the series was performed in July 2002 with the assistance of an expert mentor. One senior operator performed subsequent procedures. All donors were fluid-loaded intravenously before LDN with 2 L of normal saline. A combination of electrocautery and ultrasonic dissection was used to fully mobilize the kidney and isolate the renal artery, vein and ureteric bundle, taking care to maintain a large mass of peri-ureteric tissue. To this end, dissection of the hilum was restricted medial to the gonadal vein (Fig. 1). A diuresis was maintained during surgery with a combination of crystalloid, colloid and mannitol boluses, until the recipient team were ready for graft harvest. At this time the ureter, artery and vein were stapled (Endo-GIA, US Surgical Corp., Norfolk, USA) or clipped (Weck Closure systems, Research Triangle Park, NC, USA) in sequence. The kidney was then retrieved from the abdomen in a collection bag via a pre-formed (6 cm) Pfannenstiel incision. Systemic heparinization with subsequent protamine reversal, as practised by some laparoscopic teams, was not part of the retrieval protocol.

Donor mortality and morbidity are the primary concerns of surgeons harvesting live grafts, followed closely by the performance of the allograft implanted. The risk of death from donor nephrectomy has been quantified as 0.03% and attributed principally to thromboembolic complications [3,10]. Surgical outcomes predicting an increased relative risk for venous thrombosis were therefore of particular interest as surrogate markers pertaining to donor mortality.

We recorded prospectively donor and recipient demographics (age, sex, donor renal
function and weight), intraoperative variables (operative duration, blood loss, open conversion of LDN and warm ischaemia time), donor complications after surgery (including analgesia requirements) and allograft function (incidence of delayed graft function, graft loss, creatinine clearance and ureteric complications). The warm ischaemia time was recorded as the time from occluding the renal artery to immersing the kidney in ice and establishing heparinized hypothermic perfusion. Delayed graft function was defined as the requirement for dialysis in the first week after surgery.

Continuous parametric data are reported as the mean (sd) and evaluated using Student’s t-test; nonparametric data, reported as the median (range), were compared using the Mann–Whitney U-test. Categorical variables were tested for significance using Fisher’s exact test; in all tests significance was interpreted as $P<0.05$ for the two-sided hypothesis.

**RESULTS**

There were 79 individuals in the study; in one recipient of a graft, harvested using ODN, it failed at 5 days with renal vein thrombosis secondary to severe rejection. He later received a laparoscopically harvested graft (part of the study), which continues to function. There were no deaths perioperatively in either group. Eleven of the ODN group had right-sided and nine a left-sided nephrectomy.

The donors and recipients were similar for the important demographic and functional variables (Table 1). Both groups contained two children receiving adult grafts; these operations were performed in an associated institution.

No LDN required conversion to ODN; the operative duration was comparable between the procedures (Table 1). Neither group of donors required blood transfusion. The estimated blood loss and decrease in haemoglobin concentration (Table 1) were lower with LDN, but graft warm ischaemic time was significantly longer for LDN.

The minimally invasive procedure allowed both earlier mobilization and hospital discharge, although there were several minor complications (Table 1). Two patients reported excessive bruising, but both haematomas resolved quickly and spontaneously. One LDN donor was readmitted in the first week with abdominal pain, which responded to oral analgesia, and ultrasonography was unremarkable. Four laparoscopic donors developed fever after surgery; one was attributed to catheter-related cystitis and one to epididymitis. No positive cultures were reported for two patients with significant pyrexia, which responded to broad-spectrum antibiotics.

As expected, the open donors had a longer hospital convalescence and reported more

| TABLE 1 Donor and recipient demographics, intraoperative variables, donor complications and graft outcome |
|-------------------|-------------------|----------|
| Mean (SD) or median (range) | Laparoscopic | Open | P* |
| N | 20 | 20 | ns |
| Donor age, years | 52 (32–72) | 50 (25–61) | ns |
| M : F | 14 : 6 | 11 : 9 | ns |
| GFR (mL/min) | 98 (15) | 102 (18) | ns |
| Weight, kg | 80 (9) | 84 (14) | ns |
| Recipient age, year | 38 (2–68) | 37 (11–59) | ns |
| M : F | 11 : 9 | 14 : 6 | ns |
| Intraoperative first warm ischaemic time, min | 5 (2–7) | 2 (0–4) | <0.001 |
| Conversion rate | 0 | NA | ns |
| Duration, min | 165 (105–240) | 153 (110–190) | 0.27 |
| Blood loss, estimated, mL | 200 (100–600) | 350 (100–1700) | 0.01 |
| Haemoglobin loss (g/L) | 2.1 (2–2.8) | 2.3 (1–4.6) | 0.12 |
| Complications | | | |
| Patient-controlled analgesia, mg morphine | | | |
| Analgesia requirement | 19 (3–51) | Epidural | NA |
| Hospital stay, days | 3 (2–7) | 5 (2–10) | <0.001 |
| Immediate, n | | | |
| UTI | 1 | 1 | ns |
| Pyrexia of unknown origin | 2 | 0 | ns |
| Atelectasis/LRTI | 0 | 2 | ns |
| Epidymitis | 1 | 0 | ns |
| Pfannenstiel site bruising | 2 | NA | NA |
| Deep vein thrombosis | 0 | 1 | ns |
| Readmission | 1 | 0 | ns |
| At 3 months | | | |
| Incisional hernia | 0 | 1 | ns |
| ‘Bulging’ wound | 0 | 5 | 0.047† |
| Persistent wound pain | 0 | 5 | 0.047 |
| Graft outcome, n | | | |
| Delayed graft function | 1 | 2 | ns |
| Early graft loss | 0 | 2 | ns |
| Urinary complications | | | |
| Urine leak | 0 | 1 | ns |
| Vesicoureteric stenosis | 0 | 0 | ns |
| At discharge | | | |
| serum creatinine, µmol/L | 124.7 (38.4) | 126.4 (48.2) | ns |
| GFR, mL/min+ | 55.7 (26) | 55.4 (22) | ns |

*Mann–Whitney U-test; †Fisher’s exact test; ‡Cockcroft-Gault estimate calculated using donor age, recipient weight and serum creatinine concentration; LRTI, lower respiratory tract infection; ns, not significant; NA, not applicable.

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wound problems at the 3-month follow-up than those after LDN. Despite the use of epidural analgesia, two open donors developed pulmonary complications and one required a period of anticoagulation for a calf deep vein thrombosis.

Overall there were two early graft losses caused by severe acute rejection in the ODN group, and none in the LDN group (Table 1). Two recipients after LDN also had severe acute rejection. In these cases rescue therapy with a T-lymphocyte polyclonal antibody (Thymoglobuline, Sangstat, Lyon, France) was successful. Early graft function, as measured by the incidence of delayed graft function, serum creatinine concentration and GFR, appeared to be unaffected by the longer warm ischaemic time (Table 1 and Fig. 2).

DISCUSSION

Living donor graft harvest stands alone as a procedure exposing an individual to major surgical harm with no anticipation of personal benefit [3]. In the UK there has been an understandable reluctance to adopt a procedure that has been associated with high rates of open conversion [12], major visceral and vascular injury [13], chylous ascites [14], and colonic injury [13]. In addition there was also evidence, from early series, of a higher rate of graft ureteric complications and delayed function [12,13,15,16]. Several variables were proposed to predict a difficult laparoscopic procedure, including obesity [17], right-sided kidneys [18] and multiple renal vessels [19]. As a consequence, and concession to donor safety, many centres adopted either hand-assisted or mini-incision techniques as either a bridge to learning LDN or a definitive procedure [11,16,20,21]. In comparison with other laparoscopic techniques, learning LDN appears to be particularly difficult and demanding [21,22]. The most successful LDN training programmes use a combination of animal-based workshops and observational human learning [6,21,22]. It was suggested that for UK centres without either large-volume laparoscopic urology or easy access to animal-based training, the safe acquisition of LDN skills may be unrealistic [10]. However, our data suggest that UK urological transplant teams can successfully introduce fully laparoscopic live DN without compromising either patient safety or graft outcomes.

For all significant outcome variables the present LDN was comparable to, or out-performed, the ODN. Importantly there was no requirement for open conversion or major intraoperative complications threatening donor safety. The shorter hospital stay, early mobilization and reduction in patient morbidity should also confer the additional benefit of lower procedure-related costs. Whilst the period of graft warm ischaemia was significantly longer for LDN, the early graft function appeared unaffected. This finding was recently reaffirmed by a report of >700 LDN procedures [13].

However, the present ODN group had a poorer outcome than could be expected from our previous experience. Two of 20 live donor-derived grafts in 2003 (90%, first-year graft survival) were lost to acute rejection and we have reviewed our immunosuppressive protocols in response.

We think that we have identified several reasons for our initial success with LDN. The first live-donor procedures were conducted after the senior operator had performed >80 laparoscopic nephrectomies as part of his general urological practice. To compound this learning experience the expert mentor present at the initial procedure was able to guide the team and pass on hard-learned lessons. The collective experience of our laparoscopic transplant urology team now includes >400 laparoscopic urological procedures; this has ensured that the skill level has been maintained and improved between relatively infrequent LDN procedures. As the level of confidence in the procedure has increased, more donors have come forward for LDN. In 2002 and 2003 we performed 18 donor nephrectomy procedures; currently we have 25 procedures scheduled for 2004.

Initially we only considered donors with a normal-sized left kidney supplied by a single artery and vein for laparoscopic donation (see methods). We are now relaxing our selection criteria, in a measured way, towards performing right-sided LDN, an approach that has historically been successful for other teams [18,23]. To date we have successfully removed two left-sided grafts with a dual vascular supply, and one graft from a 120-kg donor (body mass index 33 kg/m²) (Fig. 1); both of these anatomical features have been considered relative contraindications to LDN previously [17,18]. In this respect the transplantation background of the senior operator with experience in ODN and extensive experience of laparoscopic renal surgery has been invaluable in developing this programme.

In summary, UK centres with combined experience and volume of both laparoscopic urological surgery and renal transplantation can successfully adopt a LDN programme by initially offering the procedure to selected recipients. A graduated approach to the technical difficulties posed by LDN should not jeopardise donor safety or early graft outcome. At this early stage of our LDN programme we have already seen more potential live donors coming forward for assessment, and a similar nationwide approach could help address the current crisis in kidney supply.

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CONFLICT OF INTEREST

None declared.

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Correspondence: Colin H. Wilson, The Department of Urology, The Freeman Hospital, High Heaton, Newcastle-upon-Tyne, NE7 7DN, UK.
e-mail: c4moon@doctors.org.uk

Abbreviations: L(O)DN, laparoscopic (open) donor nephrectomy.
Simultaneous bilateral percutaneous nephrolithotomy in children

MORSHEM A. SALAH, BÉLA TÁLLAI, ENDRE HOLMAN*, MUNIM A. KHAN†, GYÖRGY TÓTH and CSABA TÓTH

Department of Urology, Medical and Health Science Center, University of Debrecen, Debrecen, *Department of Urology, Semmelweis Hospital, Kiskunhalas, Hungary, and †Department of Urology, Millat Hospital, Sadakabad, Pakistan

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OBJECTIVE

To evaluate the efficacy of removing bilateral kidney stones simultaneously from children, in one session.

PATIENTS AND METHODS

Thirteen patients (three girls and 10 boys, 26 kidneys; mean age 8 years, range 3–14) underwent simultaneous bilateral percutaneous nephrolithotomy (PCNL) in the same session, under general anaesthesia, starting with ureteric catheter insertion into both kidneys and using a 26 F adult nephroscope. The mean (range) stone diameter was 2 (1–3.5) cm. Three patients had staghorn stones in one of their kidneys. Ultrasonic disintegration was used; two patients had bilateral and two others unilateral endopyotomy, and one patient had percutaneous suprapubic cystolithotomy in the same session. The mean (range) operative duration was 65 (55–90) min.

RESULTS

All patients were rendered stone-free; there was no severe bleeding or any other complication. On one side in one of the patients, a second session was needed because of residual stone. The nephrostomy tubes were removed 3 and 4 days after PCNL and the hospital stay was 6 (1–11) days.

CONCLUSION

The advantages of simultaneous bilateral PCNL are reduced psychological stress, one cystoscopy and anaesthesia, less medication and a shorter hospital stay and convalescence, with considerable savings in cost. In experienced hands this method can be used not only in adults but also in children. To our knowledge this is the only report of this technique in children.

KEYWORDS

simultaneous PCNL, paediatric, urolithiasis, outcome

INTRODUCTION

Since the early 1980s when percutaneous nephrolithotomy (PCNL) was introduced, open surgical procedures have virtually been replaced in adults. This technological advance was slowly applied in children, primarily because of the technical limitations associated with smaller patients and secondly because of the rarity of paediatric urolithiasis. Simultaneous bilateral PCNL (SBPCNL) was reported in adults [1–8]. SBPCNL in children is a challenge for the endourologist; to our knowledge, we report the first series in children.
PATIENTS AND METHODS

Between January 1998 and December 2002, 13 children (three girls and 10 boys, 26 kidney units; mean age 8 years, range 3–14) with bilateral kidney stones were treated by SBPCNL. The mean (range) stone diameter was 2 (1–3.5) cm; three patients had staghorn stones in one of their kidneys (Fig. 1a).

SBPCNL was conducted with the patients under general anaesthesia; in the lithotomy position a paediatric cystoscope was inserted into the urinary bladder and 4–5 F ureteric catheters inserted into both kidneys, and fixed to an 8–10 F Foley bladder catheter. The patient was then turned prone, and both kidney areas disinfected and isolated. The operation began with the side containing the larger stone. Contrast material, previously dyed with methylene blue, was given through the ureteric catheter to make the collecting system visible under fluoroscopy. An 18 G needle was used to puncture the collecting system. The lower or middle calyx was punctured, depending on the location of the stone. When the needle was safely positioned in the collecting system (from the appearance of methylene-blue contrast material through the needle), a 0.9 mm guidewire was inserted through the needle into the collecting system. After making a small skin incision, the needle was removed. The nephrostomy tract was dilated with metal dilators up to 23 F, then a 26 F adult nephroscopic sheath inserted above the last dilator, the dilators removed and the nephroscope inserted. The dilatation procedure was controlled under fluoroscopy. Isotonic saline was used for irrigation and visualization. The large and staghorn stones were crushed with an ultrasonic disintegrator, small stone fragments removed by suction, and larger fragments with stone forceps. At the end of the procedure an 18 F nephrostomy tube was left through the nephroscope sheath. The nephrostomy tube provided compression to avoid bleeding after the procedure, and helped the drainage of blood-stained urine and clots soon after surgery. There was no severe bleeding alongside the 18 F nephrostomy tube.

After finishing one side the surgeon changed position, and the mobile fluoroscope and all instrumentation were moved to the contralateral side, and the procedure repeated. In one patient, when a second session was necessary, no ureteric catheter was inserted, as the patient had a nephrostomy tube and thus contrast material was delivered through the tube the tract re-dilated as usual.

Two patients had bilateral and two others unilateral PUJ stenosis, and had an endopyelotomy in the same session. The ureter was stented with a paediatric JJ catheter for 6 weeks. One patient had a percutaneous suprapubic cystolithotomy in the same session for a urinary bladder stone.

RESULTS

The mean (range) operative duration was 65 (55–90) min; all patients were eventually rendered stone-free (Fig. 1b), with one patient having a residual stone on one side, requiring a second session 6 days after the first. There was no severe bleeding or any other complication, and no blood transfusion was required; the mean decrease in haemoglobin was 1.73 g/L.

The ureteric catheters and bladder catheter were removed on the first day and patients assessed by a plain abdominal film and ultrasonography on the second day. If there was no residual stone and the urine from the nephrostomy tubes was clear, the nephrostomy tubes were clamped and removed at 3 and 4 days, respectively. The plain film was repeated after removing the nephrostomy tubes (Fig. 1b).

Patients were discharged 4 or 5 days after PCNL; in one patient the ureteric catheters and bladder catheter were removed on the day of PCNL, as the urine was clear in both nephrostomy tubes and the plain film was negative, and the patient was discharged on the same day. The mean (range) hospital stay was 6 (1–11) days. The JJ ureteric stents were removed after 6 weeks.

Stone analysis showed cystine and calcium oxalate mono- and dihydrate in one patient each, ammonium urate in two and mixed calcium oxalate and uric acid in nine. One patient with a cystine stone had a recurrence on one side after 2 years, treated by PCNL. All of the six endopyelotomies appeared to be successful, as assessed by IVU at 1 year, but could not be validated statistically because there were too few patients.

DISCUSSION

Bilateral stones in children are challenging for the endourologist; although ESWL is the first choice for most the upper urinary tract stones, for those >1.5 cm or dense stones the success rate of ESWL decreases. The clearance rate is also less in children than in the adults, reported as 45–82%, but as low as 28% in some reports [9–11].

To attain a high stone-free rate requires more sessions for larger and/or dense stones, but the need for auxiliary procedures [12] and the chance of complications also increases. The late biological effects of ESWL in children
remain controversial, e.g. changes in predicted renal growth rates were reported recently [13].

As experience is gained in percutaneous stone surgery there is continuous improvement in the success rate and a decrease in operating time, complication rate and hospital stay after treatment.

We have used PCNL in >6000 adults and >300 children before attempting simultaneous bilateral PCNL. In our experience we have had no complications related to the relatively large instruments (26 F nephroscope) [14]. We felt able to use SBPCNL in children after >150 successful interventions in adults; the previous study in adults showed no significant difference in laboratory values and complications between SBPCNL and unilateral PCNL [7,8]. The planned bilateral procedure should not be continued if there is any complication on the initial side; the contralateral side is better postponed for a separate session.

After endopyelotomy there was no recurrent PUJ obstruction after 1 year in the three patients treated. Because of the few patients and the short follow-up the results cannot be assessed statistically, but in our previous report the success rate was 86–89% in adults and children [15–17].

Two patients had ammonium urate stones, probably of a nutritional origin; to reduce the occurrence of such acid urate crystals, mother’s milk should be supplemented with additional food from infancy, possibly by mass education and eradication of poverty in the developing world.

Almost all of the present interventions were in Yemen and Pakistan; thus social customs were respected, as most of these patients came from remote villages, where there were no healthcare services within a reasonable distance, and thus there were no facilities for a rigorous follow-up. Another important reason for using endoscopic stone removal as the primary management was financial, as there is no health insurance in Yemen and Pakistan, and the parents were able to pay only for one definitive procedure.

In conclusion, the advantages of SBPCNL are evident; one preparation, minimized psychological stress, one cystoscopy and anaesthesia, one (shorter) hospital stay and convalescence, less medication and considerable cost saving. In experienced hands and with selected cases, this method can be used not only in adults but also in children.

**CONFLICT OF INTEREST**

None declared.

**REFERENCES**


Correspondence: Morshed A. Salah, Department of Urology, Medical and Health Science Center, University of Debrecen, Nagerderi krt. 98, 4032 Debrecen, Hungary. e-mail: morshed@jaguar.unideb.hu

Abbreviations: (SB)PCNL, (simultaneous bilateral) percutaneous nephrolithotomy.
The role of unilateral nephrectomy in the treatment of nephrogenic hypertension in children

NAVROOP S. JOHAL, DAVID KRAKLAU and PETER M. CUCKOW
Department of Paediatric Urology, Great Ormond Street Hospital, UK

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OBJECTIVES
To define the efficacy of unilateral nephrectomy in a large series of patients presenting with renal disease and hypertension, as the latter may be a prominent finding in children with nephrourological disease (renal parenchymal disease, renovascular disease, obstruction, renal dysplasia and cancer).

PATIENTS AND METHODS
We retrospectively reviewed the hospital and outpatient records of 118 children who presented for evaluation with hypertension, and who had a nephrectomy between 1968 and 2003. Patients included in the study were those who had a unilateral nephrectomy for benign renal hypertension with a normal contralateral kidney; in all, 21 had complete records and follow-up were evaluated. The hypertension was associated with primary renal disease, obstruction and renovascular disease. Blood pressure and medication requirements were compared before and after surgery, the blood pressure values also being compared with published nomograms.

RESULTS
Patients were diagnosed with hypertension at a median age of 5 years and had a nephrectomy at a median of 11 months after the diagnosis. The median follow-up after surgery was 39 months. Most patients responded well and became normotensive, or there was a reduction in the need for medication. The median time to normalization was 2, 10 and 11 days in patients with primary renal disease, obstruction and renovascular disease, respectively.

CONCLUSION
Nephrectomy is successful in normalizing blood pressure in children with benign renal hypertension and with a normal contralateral kidney.

KEYWORDS
kidney, hypertension, nephrectomy, children

INTRODUCTION
Hypertension is less commonly diagnosed in children than in adults, and is a sign of identified (secondary hypertension) or unidentified pathophysiology (primary or essential hypertension). A high blood pressure may be identified at a more advanced stage in children, with resultant significant morbidity [1].

Renal hypertension is the most common cause of paediatric hypertension [2]; the prevalence in children is 0.5–1.5% [3]. Significant hypertension is defined as persistently elevated systemic blood pressure of >95th percentile for age and height [4]. Secondary hypertension from potentially correctable surgical causes, e.g. renal parenchymal or renovascular disease, decreases with age and accounts for half in neonates but only 5% in adolescents [3]; this compares to <3% in adults [3]. The specific causes of secondary hypertension include congenital conditions such as co-artcation of the aorta, and acquired conditions such as cancer, adrenal disease, renal parenchymal disease and renovascular disease [3].

Children with hypertension are often asymptomatic, but when symptoms are present they can include headache, dizziness, visual changes, failure to thrive, mental status changes or seizures, weakness, chest pain or the sequelae of heart failure. The aim of the current study was to define the success of nephrectomy for treating hypertension in children with unilateral disease and a normal contralateral kidney.

PATIENTS AND METHODS
We retrospectively reviewed the hospital and outpatient records of 118 children who presented for evaluation of hypertension to the paediatric nephrologists, and who had a nephrectomy between 1968 and 2003. In all, 21 patients had complete records and had a unilateral nephrectomy for benign renal hypertension. All these patients had a normal contralateral kidney and were followed and evaluated. Excluded were patients with tumour as a cause of the hypertension and those with end-stage renal insufficiency.

Blood pressures were compared with published nomograms. All patients were hypertensive (>95th percentile for age and height) despite antihypertensive medication. Their age at diagnosis, time to therapy, medication requirement before and after surgery, and histological diagnosis, were compared.

The preoperative medications included hydralazine, phenoxybenzamine, nifedipine, captopril, enalapril, atenolol, propranolol, chlorothiazide, frusemide, and minoxidil. One patient had not yet been initiated on antihypertensive therapy, a neonate who presented with a UTI, fever and hypertension secondary to an infected multicystic dysplastic kidney. Ten patients were on two medications, five were taking three and three were on four.

Many vascular and renal parenchymal abnormalities were identified histologically...
Vascular anomalies included renal artery minimally functioning kidneys with evidence not (eight) with VUR. Three patients had atrophic, scarred kidney associated (one) or (Table 1). The most common diagnosis was an angiography, and renal vein renin and peripheral renin measurements.

The overall outcome measures were a normalization of blood pressure and reduction in antihypertensive medication. Complete success was considered in children off all medications and partial success was determined as a reduction in the medications required to maintain a normal blood pressure.

RESULTS

The median age at presentation with hypertension was 5 years (range, birth to 12 years). The median (range) time from the initial diagnosis of hypertension to the date of surgery was 11 (0–105) months and the follow-up after surgery 39 (1–168) months. All patients had blood pressures consistently >95th percentile for age and height. The highest recorded blood pressure was 250/170 mmHg in a patient with fibromuscular dysplasia.

The medication requirements were less after surgery, with most patients (16 of 21) having a normal blood pressure when completely off medication. One patient required one medication and four continued on two. All but one of these patients had a reduction in the amount of medication; the exception with stable medication had a nephrectomy for a nonfunctioning kidney, but later had end-stage insufficiency in the remaining kidney.

<table>
<thead>
<tr>
<th>Histological cause</th>
<th>N patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrophic scarred kidney</td>
<td>1</td>
</tr>
<tr>
<td>reflux related</td>
<td>8</td>
</tr>
<tr>
<td>no reflux</td>
<td>3</td>
</tr>
<tr>
<td>Obstruction</td>
<td>1</td>
</tr>
<tr>
<td>Multicystic dysplastic kidney</td>
<td>8</td>
</tr>
<tr>
<td>Renovascular disease</td>
<td>1</td>
</tr>
</tbody>
</table>

(Table 1). The most common diagnosis was an atrophic, scarred kidney associated (one) or not (eight) with VUR. Three patients had minimally functioning kidneys with evidence of PUJ obstruction and one infant had a multicystic dysplastic kidney.

Vascular anomalies included renal artery stenosis (two), renal vein thrombosis (one), renal artery thrombosis (one), fibromuscular dysplasia (two), renal artery aneurysm (one), and renal artery dysplasia (one). The diagnosis of renovascular disease was made after angiography, and renal vein renin and peripheral renin measurements.

The final histological diagnosis of the 21 patients and was dependent on dialysis at the long-term follow-up.

Sixteen of the 21 patients had complete normalization of blood pressure, one no change and four were deemed a partial success. The median (range) time to normalization of blood pressure was 7 (1–120) days; the value varied among the different pathological groups. Those with atrophic kidneys normalized at a median of 2 (1–28 days), compared with 10 (9–11) and 11 (1–112) days in the obstructive and renovascular patients, respectively.

DISCUSSION

Of children with secondary hypertension, 75–80% have a renal abnormality and therefore it is essential to evaluate the urinary tract early after the confirmed diagnosis of elevated blood pressure [5]. After confirming significant hypertension, initial studies should include serum electrolytes, creatinine and catecholamines [6]. As is true for many paediatric urological problems, renal ultrasonography is often the first imaging study. In all of the present patients this study identified at least one abnormality.

The 'reference' standard radiographic test for investigating renovascular hypertension remains intra-arterial digital subtraction angiography, but newer techniques, e.g. the MR angiogram, may replace this [6,7]. Useful adjuncts may include renal-vein renin determinations, duplex ultrasonography, and captopril-enhanced renal scintigraphy [7]. Six of the present patients were diagnosed with a renovascular cause for their hypertension after angiography and renal-vein renin measurements. Of the two who had peripheral renin determinations, one was elevated and the other normal. Peripheral renin activity maybe helpful but is not always diagnostic of renovascular hypertension [5]. Selected renal-vein renin determinations were suggestive of unilateral disease in three patients, equivocal in one and inconsistent in one. This test, if inconclusive (as shown in two of the patients), does not exclude renin participation in the cause of and maintenance of hypertension [6].

In patients with hypertension and a minimally functioning abnormal kidney it may be unnecessary to use angiography and selective renin determinations. In other groups these may have some use, as they have a higher specificity and sensitivity than in adults [6].

The goal of therapy for children with hypertension from a renal cause is to improve or cure the high blood pressure and preserve renal function [7]. The relative and absolute indications for intervention are ill-defined but include poor control with medication, decrease in renal function, unilateral abnormality, and end-stage renal disease [8]. The question remains about when to intervene to potentially reduce the requirement of life-long medications, with their potential side-effects.

Percutaneous transluminal angioplasty may be attempted for discrete, non-ostial stenoses secondary to fibromuscular dysplasia. Longer lesions may require open surgical revascularization. Chalmers et al. [9] examined 10 children and young adults with renovascular hypertension and a well-functioning affected kidney. Patients had fibromuscular dysplasia, mid-aortic syndrome and neurofibromatosis. They reported success in only one of three after balloon angioplasty. Other patients in the series had a vascular bypass or auto-transplantation. Of these, seven became normotensive and were off all medications, and two had a partial response. The authors emphasized that careful selection of young patients with renovascular hypertension treated surgically gave durable positive results. Stanley et al. [10], examined the 3-year experience of surgical therapy for renovascular hypertension, concluding that children with hypertension caused by discrete vascular lesions benefit from their correction, providing there is good preoperative ipsilateral renal function.

Nephrectomy is successful and the treatment of choice in the unilateral minimally functioning kidney with a normal contralateral kidney. The present results of complete cure in 16 of 21 (76%) and a 95% overall success rate compares favourably with other studies of nephrectomy in patients with unilateral renal parenchymal disease and a
normal contralateral kidney [8,11]. Wanner et al. [11] reported a complete cure in more than half of a similar population. More recently, Baez-Trinidad et al. [8] reviewed patients who had a nephrectomy for renovascular hypertension and with a normal contralateral kidney; all patients had partial or complete resolution of the hypertension. Their complete cure rate was 75% and all the patients maintained normal renal function. It is critical to maintain extended surveillance, as possible long-term consequences after nephrectomy include nephrosclerosis, proteinuria and renal insufficiency [8].

In conclusion, nephrectomy is successful in normalizing blood pressure in children with nephrogenic hypertension. Patients with a unilateral renal abnormality and hypertension may benefit from early nephrectomy, to reduce the morbidity from high blood pressure and hypertensive medication.

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CONFLICT OF INTEREST

None declared.

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Correspondence: Navroop Johal, Department of Paediatric Urology, Great Ormond Street Hospital, UK.

e-mail: navjohal@hotmail.com
Growth and stretch response of human extrophy bladder smooth muscle cells: molecular evidence of normal intrinsic function

ANNA ORSOLA*, CARLOS R. ESTRADA, HIEP T. NGUYEN, ALAN B. RETIK, MICHAEL R. FREEMAN, CRAIG A. PETERS and ROSALYN M. ADAM

Urological Diseases Research Center, Department of Urology, Children's Hospital Boston and Harvard Medical School, Boston, MA, USA
*Current address: Urology Department, Clínica Plató, C/Plató 21, Barcelona, Spain

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OBJECTIVE
To establish primary cultures of smooth muscle cells (SMC) from human extrophic bladders (E-SMC), and determine their in vitro growth dynamics and responses to mechanical stretch.

MATERIALS AND METHODS
Primary cultures of E-SMC from three patients were established from extrophic bladder tissue using an explant method. Growth dynamics were assessed using tetrathiazolium-dye uptake. The DNA synthesis rate in response to cyclic stretch-relaxation was determined with thymidine-incorporation assays. Expression of the SMC mitogen heparin-binding epidermal growth factor-like growth factor (HB-EGF) mRNA in response to mechanical stretch was determined using semiquantitative reverse transcription-polymerase chain reaction.

RESULTS
The approximate doubling time of the E-SMC grown in the presence of serum was 4 days, consistent with growth rates of SMC reported previously. E-SMC exposed to stretch had greater DNA synthesis, albeit to a lesser extent than previously seen with non-extrophic SMC. The expression of HB-EGF was also increased in cells exposed to mechanical stimuli, consistent with our previous finding of stretch-regulated HB-EGF gene expression in bladder SMC.

CONCLUSIONS
E-SMC had growth characteristics similar to those previously reported in non-extrophic cells. E-SMC also had stretch-induced expression of HB-EGF mRNA. These observations provide evidence that despite development in an abnormal defunctionalized state, E-SMC retain the potential for normal growth, and may modulate this response through mechanisms similar to those operating in normal bladder SMC.

KEYWORDS
bladder extrophy, HB-EGF, stretch, primary culture, smooth muscle

INTRODUCTION
Reconstruction of the extrophied bladder is based on the assumption that the detrusor, after being defunctionalized during fetal life, can undergo normal growth and development after surgical repair [1,2]. With appropriate outlet resistance it is thought by some that the small defunctionalized bladder can expand to provide adequate storage of urine, develop functional detrusor muscle, and acquire urinary continence [3,4]. The requisite outlet resistance can be created by reconstructing the bladder neck immediately after birth, at the time of bladder closure (as in the neonatal total reconstruction technique) or postponed in the staged approach [2,5].

Clinically, continence is achieved when the bladder begins storing urine [6–8]; this clinical observation supports the hypothesis that the extrophic bladder has the potential for normal function if bladder cycling is restored. Some authors contend that a more rapid onset of continence and increased continence rates are achievable with earlier initiation of urine storage, and therefore advocate the complete neonatal one-stage closure [1,2]. However, normal bladder function is not a certainty in either the early or staged reconstruction, and extrophy remains a substantial clinical challenge.

Central to the debate about the timing of bladder neck reconstruction is the intrinsic potential of extrophic bladder cells for normal development, which has not been examined experimentally. In broad terms this begs the question of whether the extrophic bladder is normal but in an abnormal situation, or is intrinsically abnormal. Unfortunately, there are few basic studies of the human extrophic bladder, with limited experimental systems and methods.

To address this need, we isolated and propagated primary cultures of bladder smooth muscle cells from neonatal extrophic bladder tissue (E-SMC). Using these cells we addressed the following questions: (i) are growth patterns of E-SMC similar to patterns described in previous studies of non-E-SMC; and (ii) are E-SMC responsive to mechanical stimuli in a fashion similar to non-extrophic bladder SMC, as previously reported in our laboratory? The answers to these questions may support the optimistic hypothesis that extrophic bladders are capable of normal growth.

MATERIALS AND METHODS
After obtaining parental consent and institutional review board approval, biopsies were obtained from three newborn children [1 day old, two boys and one girl] having their bladder extrophy closed. E-SMC were isolated and propagated in culture by the...
expplant method, as described previously for non-E-SMC [9, 10]. Briefly, bladder tissue specimens were immediately dissected to isolate the detrusor layer, and then finely chopped. The pieces of about 2 mm were placed on a scored cell-culture dish and allowed to briefly air-dry for adherence. Dulbecco’s modified Eagle’s medium (DMEM, Gibco/Life Technologies, Gaithersburg, MD) supplemented with 10% fetal bovine serum (FBS, HyClone Laboratories, Logan, UT), penicillin (100 U/mL) and streptomycin (100 μg/mL) was added, and cells maintained in this medium. All experiments were done in triplicate on cells between passages 2 and 5.

Primary cultures were characterized as SMC by morphological criteria and by expression of specific SM markers by immunocytochemistry. Mouse monoclonal antibodies to SM markers were: anticalponin (clone hCP, 1:600 dilution), anti-SM-α-actin (clone hSM-V, 1:500 dilution), and anti-SM-myosin (clone hSM-V, 1:500 dilution). To confirm the absence of endothelial cells, anti-CD-31 (clone WM-59, 1:100 dilution) was used. All primary antibodies were purchased from Sigma Chemical Co. (St. Louis, MO). Cells incubated with no primary antibody served as a negative control. Slides were incubated with an antimonospecific biotinylated secondary antibody (included in the Vectastain Elite ABC Kit, Vector Labs, Burlingame, CA) and immunoreactivity visualized using the ABC Kit, as described previously [9].

Growth of the E-SMC under steady-state conditions was assessed using the uptake of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) dye to measure cell viability, as described previously [11]. Cells were seeded at 1 × 10^4/well in 24-well culture plates in DMEM/10% FBS, and assayed at selected times. Viability was determined by adding MTT (0.5 mg/mL final concentration) to cells for 4 h; incorporated dye was eluted from cells with isopropanolol/0.1 mol/L HCl, and dye absorbance determined at 570 nm, with background correction at 655 nm, using a microplate reader (Bio-Rad Laboratories, Hercules, CA). Dye absorbance is directly proportional to cell number.

To assess cyclic stretch-relaxation of E-SMC, the cells were seeded at 8 × 10^4/well in six-well silicone elastomer-bottomed culture plates coated with collagen type I (Bioflex, Flexcell, Hillsborough, NC). Cells were grown to near confluence and then rendered quiescent by incubating for 24 h in reduced-serum medium. Cells were subjected to continuous cycles of stretch-relaxation using a computer-driven, vacuum-operated stretch-inducing device (Strain Unit FX-3000, Flexcell) as described [12, 13]. Each cycle consisted of 5 s of stretch and 5 s of relaxation (0.1 Hz), inducing different percentages of deformation up to ~25% maximum radial stretch at the periphery of the membrane. E-SMC incubated in parallel but with no exposure to stretch served as controls. The DNA synthesis rate of E-SMC exposed to mechanical stretch was determined using a thymidine-incorporation assay, as previously described [10].

Semi-quantitative RT-PCR was used to assess the relative levels of heparin-binding epidermal growth factor-like growth factor (HB-EGF) and glyceraldehyde-3 phosphate dehydrogenase (GAPDH) mRNA in E-SMC exposed to cyclic-stretch relaxation. After stretch stimulation, cells were harvested at selected times (0–24 h) and total RNA extracted using the RNeasy RNA extraction kit (Qiagen, Chatsworth, CA) according to the manufacturer’s instructions. mRNA was reverse transcribed and cDNA amplified as described previously [13]. PCR products were resolved by acrylamide-gel electrophoresis and signals visualized after exposure of dried gels to X-ray film. Normalization to GAPDH expression and limiting dilutions of cDNA enabled semiquantitative comparisons between samples after densitometric measurement of intensities using an image-analysis system.

**FIG. 1. Immunocytochemical staining of E-SMC for SM-α-actin and calponin. E- and non-E-SMC stained positively for the SM-α-actin and calponin.**

<table>
<thead>
<tr>
<th>Control SMC</th>
<th>α-SM-actin</th>
<th>Calponin</th>
</tr>
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<tbody>
<tr>
<td>Negative control</td>
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</table>

**RESULTS**

Based on morphological criteria and immunocytochemical staining patterns, the E-SMC lines had characteristics consistent with SMC. The samples were compared to non-exstrophic human bladder SMC; all SMC stained positively for the specific markers α-SM-actin, SM-myosin and calponin (Fig. 1). All stained negatively for the endothelial marker CD31 (data not shown), confirming the absence of endothelial cell contamination of the cultures. Cells were also confirmed as expressing myosin by immunoblot analysis (data not shown).

As shown in Fig. 2, the three E-SMC cultures had similar growth patterns under steady-state conditions. The approximate doubling time of the cells was 4 days, consistent with our previous experience of a 4-day doubling time with human non-E-SMC [9, 10].

We previously showed that cyclic stretch-relaxation of paediatric human bladder and neonatal rat bladder SMC promotes selective increases in gene expression and DNA synthesis [12, 13]. Stretch stimulated an increase in DNA synthesis in all E-SMC lines (Fig. 3) at 48 h; E-SMC line 1 doubled the synthesis, whereas line 2 and 3 had a 1.5- and 1.4-fold increase, respectively.

In addition to inducing DNA synthesis, we previously showed that HB-EGF expression can be induced in bladder SMC in response to mechanical stretch. As shown in Fig. 4, cyclic stretch of SMC induced HB-EGF mRNA in a time-dependent manner in both control SMC and E-SMC to a similar
extent. Densitometric analysis indicated that the peak HB-EGF mRNA expression was at 4–6 h after initiating stretch, consistent with previous data [12]. These data suggest that E-SMC retain the differentiated and highly specialized ability to respond to stretch by up-regulating expression of HB-EGF mRNA.

**DISCUSSION**

In the present study, E-SMC proliferated in culture and synthesised DNA in response to mechanical stretch. Furthermore, stretch increased the expression of HB-EGF mRNA in E-SMC, consistent with a previous report that HB-EGF is a stretch-responsive gene in bladder SMC [12]. These data provide further evidence that E-SMC retain normal SMC characteristics, as first shown by Lai et al. [14]. In that study, primary culture E-SMC expressed α-actin and myosin, and developed contractile properties in a fashion indistinguishable from normal bladder SMC.

To model the urodynamic environment experienced by the closed exstrophic bladder plate, we used an in vitro strain-transducing system that has been widely used to study the effects of mechanical stimulation on cells grown in monolayer culture. We consider this an appropriate experimental system in which to study bladder SMC responses to deformation. However, caution is necessary when extrapolating data obtained from stretch experiments in vitro to the clinical situation, as all in vitro studies are limited by factors such as type of growth media used and isolation of cells from their in vivo environment. In addition, cyclic stretch experiments are limited by the unknown relevance of stretch parameters to in vivo bladder distension.

For the present study, SMC were isolated from the extrophic bladders of neonates. E-SMC behave similarly to non-E-SMC assessed in previous studies, in which SMC were obtained from bladder tissue of patients undergoing ureteric reimplantation. The growth and stretch response characteristics of these cells serve as reasonable reference points for the current study, as it was not possible to obtain bladder biopsies from normal neonates for direct comparison. Despite the potential concerns over the age difference of the patients supplying the present E-SMC and the non-E-SMC studied previously, and that SMC from a refluxing bladder may behave abnormally, this population of SMC is nevertheless the best available for comparing a functional and nonfunctional bladder.

Stretch stimulation of E-SMC induced the expression of HB-EGF mRNA, consistent with previous in vitro [12] and in vivo [9] findings. HB-EGF has been described as a potent mitogen for SMC, and we previously showed that exogenous HB-EGF stimulates the proliferation of bladder SMC in culture [9,13]. In turn, increased levels of HB-EGF mRNA in SMC exposed to stretch may predict an increase in HB-EGF protein levels that could potentially act as an autocrine mitogen. Thus, the findings of similar growth rates and response to mechanical stimuli between our previous non-E-SMC and the present E-SMC seem to support the hypothesis that E-SMC retain the capacity to propagate and function well in the early postnatal period. Whether this functional capacity diminishes with time remains to be addressed experimentally and in studies of clinical outcome.

There is strong evidence that mechanical stretch is necessary for bladder growth and remodelling throughout life. With the initiation of urine production during fetal development, the bladder wall begins to undergo pressure-volume work, resulting in a parallel increase in compliance [15]. The neonatal exstrophic bladder is not yet functional, never having been exposed to the mechanical stimuli associated with filling and emptying. Using an animal model, it was postulated that this limitation compromises SMC differentiation [16]. This would explain the initial relative decrease in SM content of...
these bladders. Interestingly, after closure, the index of SM to connective tissue content increases [17,18]. These findings support our observation that exposure of E-SMC to mechanical force increases proliferation, as reported previously with control SMC [10] and in vivo models [19]. Furthermore, in the human fetus, increased bladder pressure (outlet obstruction) was reported to be linked to increased SM content [20].

Human bladder E-SMC have not been previously analysed for specific growth patterns and expression of known SMC mitogens. Current data are available only in a non-exstrophic guinea pig model, in which some cellular and molecular responses in detrusor muscle were shown to be age-specific [21]. However, extrapolating these data to human bladder exstrophy requires caution. Further study of human E-SMC is necessary before clinical and laboratory data can be complementary in formulating evidence-based treatment algorithms. In addition, the identification of specific molecular defects and their level of expression may explain the widely variable and unpredictable clinical behaviour of exstrophic bladders, and potentially allow the development of pharmacological strategies to reverse the detrimental effects of diminished bladder function in these patients.

We showed that neonatal bladder E-SMC proliferate in response to mechanical stretch and have greater DNA synthesis and HB-EGF expression, consistent with our previous studies of bladder non-E-SMC. Although the mechanism producing increased capacity after bladder exstrophy closure and functionalization remains unclear, our findings suggest that E-SMC are not intrinsically defective, and retain the capacity to respond to mechanical stretch. Currently, the surgical approaches to bladder exstrophy differ mainly in the age at which outlet resistance is restored, and thus the development of a normal pattern of bladder cycling. Whether the capacity for normal function is diminished in an age-dependent fashion remains to be investigated. The inconsistent clinical outcomes with bladder exstrophy suggest the need for adjunctive interventions to facilitate normal development and function. Finally, greater understanding of the subtle relationship of bladder function and development will inevitably improve understanding of a wider scope of bladder disorders.

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CONFLICT OF INTEREST


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Correspondence: Rosalyn M. Adam, Children’s Hospital Boston, Urological Diseases Research Center, 300 Longwood Avenue, Enders Research Building 1077, Boston, MA 02115, USA. 
e-mail: rosalyn.adam@childrens.harvard.edu

Abbreviations: (E)-SM(C), (exstrophic) smooth muscle (cells); DMEM, Dulbecco’s modified Eagle’s medium; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; GAPDH, glyceraldehyde-3 phosphate dehydrogenase; HB-EGF, heparin-binding epidermal growth factor-like growth factor.
Inhibitory actions of calcitonin gene-related peptide and capsaicin: evidence for local axonal reflexes in the bladder wall

JAMES I. GILLESPIE

The Urophysiology Research Group, School of Surgical and Reproductive Sciences, The Medical School, The University, Newcastle upon Tyne, UK

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OBJECTIVES

To explore the actions of capsaicin and the neurotransmitters released by capsaicin (substance P and calcitonin gene-related peptide, CGRP) on the phasic contractile activity generated in the whole isolated guinea pig bladder by muscarinic stimulation, and to examine the hypothesis that collateral fibres of sensory axons contribute to a local reflex in the bladder wall.

MATERIALS AND METHODS

All experiments used whole isolated bladders from female guinea pigs (270–300 g). Bladders were cannulated via the urethra to measure intravesical pressure and suspended in a heated chamber containing oxygenated Tyrode’s solution at 33–35 °C. All drugs were added to the solution bathing the abluminal surface.

RESULTS

Application of capsaicin (10 μmol/L) to the whole isolated bladder resulted in complex changes in the frequency and amplitude of phasic activity generated by muscarinic stimulation; an initial burst of activity involving a rise in frequency, a second phase of reduced amplitude and frequency and a third phase where the amplitude of the transients recovered and the frequency increased. Capsaicin had no effect on the phasic activity generated by the nicotinic ligand lobeline (30 μmol/L). As capsaicin releases the neurotransmitter content of the sensory nerves, experiments explored the actions of CGRP and substance P on the muscarinic-induced activity. CGRP (3–30 nmol/L) reduced the amplitude and slowed the frequency of the phasic activity. On washing off CGRP the amplitude and frequency of the transient activity recovered and there was a transient increase in frequency above the levels before stimulation. There was also evidence of a desensitization to CGRP on repeated application. In contrast, substance P (100–300 nmol/L) increased the frequency of the transients, while on removing it there was an inhibition of both amplitude and frequency.

CONCLUSIONS

These results suggest that neurotransmitters released from sensory nerve endings in the guinea pig bladder wall affect phasic activity. The direct application of CGRP inhibited phasic activity while substance P was excitatory, indicating the specific contributions of these neurotransmitters. The excitation after stimulation with CGRP and inhibition with substance P may indicate that these neurotransmitters feed back on the sensory nerves to induce transmitter release. Taken together, these observations suggest the presence of a local reflex in the bladder wall, where axon collaterals of afferent sensory fibres innervate the pacemaker mechanism in the bladder wall responsible for generating phasic activity. The possible importance of this reflex in the physiology and pathophysiology of the bladder is discussed.

KEYWORDS

whole bladder, guinea pig, capsaicin, CGRP, substance P, local reflex
overviews of substance P and CGRP fibres in the bladder, their distribution, species variation and release [15–20]. Sensory nerves are present within the urothelium, the suburothelial layer, the surface of muscle bundles, intramural ganglia and blood vessels [16–18]. The precise function of these neurotransmitters in the different regions of the bladder wall is unknown.

Both substance P and CGRP can be released from the sensory axons by nerve stimulation and chemical agents such as capsaicin [15,20]. There is now considerable evidence of the actions of the sensory neurotransmitters on isolated tissues and organs [15,16]. In general terms, substance P produces excitation and CGRP inhibition in the cells which they target [15]. The presence of a system of afferent nerves capable of releasing active neurotransmitter substances within the organs in which they originate has led to the introduction of the term ‘sensory/efferent’ functions of the afferent nerves [15,21].

Perhaps the most widely known sensory/efferent mechanism is in relation to the control of local blood flow. The existence of such a mechanism was first postulated over 100 years ago by Baylis, as a result of experiments showing that antidromic stimulation of afferent fibres resulted in local vasodilatation in the skin [22] (see also [15,21,23]). Such an arrangement can be described as a ‘local collateral axon reflex’. Although this mechanism appears to operate in the skin, its physiological role in other systems, particularly the bladder, are less well characterized. The extensive ramifications of sensory neurones expressing substance P and CGRP suggest that the efferent function of these nerves in the bladder must contribute to key physiological mechanisms. That these mechanisms have not yet been identified represents a major gap in the basic knowledge of bladder physiology.

Capsaicin induces complex effects on phasic activity in the isolated whole bladder of the guinea pig [13]. This raised the possibility that the sensory nerves in the bladder wall might have effects on the mechanism generating the phasic activity. If this idea is correct then the exogenous application of neurotransmitters released from the sensory nerves should have excitatory and inhibitory effects on phasic activity. Substance P can affect augmented phasic activity [10] but the actions of CGRP are unknown. The objective of the present study was therefore to determine the actions of topically applied CGRP in addition to substance P and capsaicin on phasic activity, and so explore the idea of a local reflex in the bladder wall.

**RESULTS**

The isolated whole guinea-pig bladder preparation can generate phasic rises in IVP, or autonomous activity, which are increased by exposure to muscarinic and nicotinic agonists, i.e. augmented activity [4,5]. When capsaicin was added to the solution bathing the whole bladder there was an immediate brief increase in phasic activity, followed by a distinct slowing and reduction in their amplitude (Fig. 1). These early changes are clear in the inset to Fig. 1, which shows the initial section of the record on an expanded time scale. With continued exposure the frequency of the transients increased to a level above the resting value and the amplitude gradually recovered to the levels before stimulation. The analysis of the accumulated data comparing the initial frequency of the transients (control) to the values immediately after capsaicin (initial burst), in the period of reduced activity (inhibitory phase) and during the recovery, are given in Table 1. Thus, capsaicin has a profound and complex effect on phasic activity in the whole bladder.

Through sensory axons in the bladder contain CGRP and substance P, and one of the initial consequences of exposure to capsaicin is the mobilization of these agents [15,16]. Thus it is likely that the complex effects of capsaicin seen immediately after application result from actions of CGRP and substance P on the phasic activity. To explore this directly, isolated whole bladder preparations were exposed to CGRP or substance P. Figure 2 shows that adding CGRP to the solution bathing a bladder activated by muscarinic stimulation resulted in a distinct slowing of phasic activity and a reduction in the amplitude of the transients. Data collected from 10 experiments analysing the actions of 10 and 20 nmol/L CGRP are shown in Table 1. At each concentration the amplitude and frequency of the transients were decreased, with greater effects at higher concentrations of CGRP. On removing CGRP the amplitude of the phasic activity recovered to control levels. During this recovery phase, in two of the five preparations in which it could be examined, the frequency was increased above the values before stimulation.

During these experiments, repeated exposures to CGRP resulted in a reduction in the magnitude of the effects, suggesting some form of desensitization. This was explored directly in three experiments, one of which is shown in Fig. 3. The preparation was initially exposed to 30 nmol/L CGRP, resulting in a slowing in the phasic activity and a decrease in the amplitude of the pressure changes. The concentration of CGRP was reduced by washing the bladder in a solution containing 4 nmol/L CGRP, during which the amplitude and frequency of the transients increased. A second application of 30 nmol/L CGRP was then given; the change in frequency and...
reduction in amplitude of the transients was noticeably less than in the initial exposure, suggesting that the receptors activated by CGRP are desensitized. This effect must therefore be considered in any experimental protocol used to investigate the actions of CGRP on the whole isolated bladder preparation.

Stimulating the hypogastric nerves to the guinea pig bladder results in a marked increase in the frequency of muscarinic-induced phasic activity [5]. Thus it was of interest to determine whether CGRP had any actions on this nerve-mediated modulation of phasic activity. Figure 4 shows the increase in frequency of phasic activity resulting from stimulating the hypogastric nerves at 6.5 Hz. In the presence of CGRP the effects of nerve stimulation were reduced.

Substance P is present in sensory nerves and may be co-localized with CGRP [16]. Figure 5 shows the effects of substance P at 100 and 300 nmol/L on the phasic activity induced by muscarinic stimulation. At both doses the frequency of the phasic activity was increased. This is clear in the analysis of the raw data, where the instantaneous frequency of the transients is determined. There was a distinct reduction in amplitude and a slowing of the phasic activity during the initial stages of washing off substance P, particularly pronounced after exposure to higher concentrations of substance P (Fig. 5B; Table 1).

Lobeline, a nicotinic ligand, produces transient activity which appears to be indistinguishable from that generated by muscarinic stimulation [2]. In three experiments capsaicin was added to preparations stimulated with 30 μmol/L lobeline; in each, capsaicin did not produce the complicated responses seen with muscarinic stimulation (Fig. 6). There was a small but insignificant increase in frequency and no indication of any inhibitory action. In previous studies there were differences in the responsiveness of bladders activated with muscarinic or nicotinic agents [10], but the reasons for this are unknown. It is likely that insights into these differences will lead to clarification and identification of the different components of the mechanisms contributing to the generation and modulation of phasic activity.

**DISCUSSION**

These results show that capsaicin induced excitation and inhibition of phasic activity, that substance P was predominantly excitatory, and CGRP had a significant inhibitory effect on phasic activity. If it is assumed that the primary action of capsaicin is to release neurotransmitters from the

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**TABLE 1** The actions of capsaicin, CGRP and substance P on phasic activity

<table>
<thead>
<tr>
<th>Agent (n)</th>
<th>Transients</th>
<th>Frequency, /s</th>
<th>Amplitude (vs control)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Capsaicin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>0.053 (0.015)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial burst</td>
<td>0.094 (0.023)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhibitory phase</td>
<td>0.026 (0.015)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recovery</td>
<td>0.071 (0.009)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CGRP</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>0.049 (0.07)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>10 nmol/L (5)</td>
<td>0.029 (0.09)*</td>
<td>0.33 (0.19)*</td>
<td></td>
</tr>
<tr>
<td>20 nmol/L (4)</td>
<td>0.023 (0.07)*</td>
<td>0.15 (0.08)*</td>
<td></td>
</tr>
<tr>
<td><strong>Substance P (application/wash)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>0.039 (0.007)</td>
<td>1.00/+</td>
<td></td>
</tr>
<tr>
<td>100 nmol/L (5)</td>
<td>0.101 (0.008)<em>/0.021 (0.007)</em></td>
<td>1.53 (0.14)<em>/0.36 (0.09)</em></td>
<td></td>
</tr>
<tr>
<td>300 nmol/L (4)</td>
<td>0.135 (0.009)<em>/0.010 (0.002)</em></td>
<td>0.70 (0.20*)/0.08 (0.01)*</td>
<td></td>
</tr>
</tbody>
</table>

*indicates significantly different from control, paired t-test (P < 0.05).
sensory nerves (substance P and CGRP) then the present data provide evidence that the mechanism generating complex phasic activity in the bladder wall may be innervated by collateral axons of afferent nerves. The precise micro-anatomical arrangement of the afferent nerves in relation to the phasic mechanisms is unknown, but possibly there is a local axonic reflex in the bladder wall (Fig. 7).

Local axonic reflexes were first described over 100 years ago, with initial observations in studies of the local vasodilatation resulting from antidromic stimulation of afferent fibres from the skin \[15,16,21,22\]. Since then, it was suggested that this micro-anatomical arrangement occurs in several tissues and organs, including the gastrointestinal tract, cardiovascular and respiratory systems and genitourinary system \[15,16\]. The widespread nature of this basic micro-anatomical arrangement has become apparent as a result of two key observations. First, that sensory nerves contain neurotransmitters, principally substance P and CGRP; and second, that exposure to capsaicin caused the release of these neurotransmitters. Many studies have examined the efferent arm of the reflex, by applying capsaicin, exogenous substance P and CGRP, and determining physiological changes in the tissues \[15,16\]. Although many of these studies show effects of capsaicin, substance P and CGRP, the physiological role of the local axonal arrangement in specific organs is still not well understood.

Capsaicin has been used in studies of bladder control to eliminate afferent nerves and so examine their role in the micturition cycle. The loss of capsaicin-sensitive sensory nerves results in a reduction in the afferent discharges contributing to bladder sensations. By reducing bladder sensation the volume of urine which triggers the micturition reflex is effectively increased \[24,25\]; thus bladder capacity is increased. Capsaicin treatment reduces tissue levels of substance P and CGRP \[15\], and it has been shown that the tissue levels of substance P correlate with the volume of urine triggering micturition, and the levels of substance P have been used to indicate the extent of sensory innervation \[24,25\]. This basic ‘cause and effect’ is the rationale for the therapeutic use of capsaicin, or its more potent counterpart resiniferatoxin, for treating bladder overactivity, sensory urge and incontinence \[23\]. Animals treated with capsaicin continue to void regularly. This has...
led to the suggestion that there are capsaicin-sensitive sensory nerves which signal information related to bladder volume to the CNS [23,26]. Most of the sensory nerves containing substance P and CGRP also weakly express neurofilaments and have conduction velocities suggesting that they are C fibres [27]. Although the sensory role and physiological importance of the capsaicin-sensitive afferent nerves in the control of the micturition cycle is now well established, the efferent functions of these nerves in the bladder remain poorly understood.

Applying substance P to isolated strips of bladder muscle generates contractions [14]. Neurokinin-2 receptors reportedly lie over the surface of the muscle [28] and it has been an implicit assumption that these receptors are involved in the initiation of contraction. Evidence supporting an action of CGRP in the bladder has been difficult to obtain. Its actions are likely to be inhibitory, as inhibition of contractile activity has been reported at other locations in the lower urinary tract, urethra [29] and ureters [30]. In the rat, CGRP fibres are found on the surface and within the muscle bundles [18], and in the guinea pig CGRP release can be detected from muscle strips [20]. In the human bladder no CGRP receptors were found to be associated with the detrusor muscle [28]. Thus, in rodents CGRP may have a direct action on the detrusor muscle. Contractions of detrusor strips from hamster induced by single electrical stimuli were reduced by CGRP, indicating a possible inhibitory action [31]. The present data show additional effects of CGRP; a profound inhibitory action of CGRP on phasic activity in the guinea-pig bladder. This emphasizes the absolute requirement to study inhibitory mechanisms in the system on which they may be acting physiologically.

FIG. 4. The actions of CGRP on nerve-evoked changes in IVP; A, shows an example of an original record. The preparation was initially stimulated at 6.5 Hz. CGRP was added to the bathing solution and the stimulation repeated. CGRP was then washed off and nerve stimulation repeated again. The horizontal broken line is drawn arbitrarily and shows the level set to analyse the instantaneous frequency of the transients. B(a) and C(a) show on an expanded scale the control response and that in the presence of CGRP. B(b) and C(b) show the respective instantaneous frequency plots for the control and CGRP conditions. Temperature 34°C.

FIG. 5. An experiment to illustrate the excitatory actions of substance P on an isolated whole-bladder preparation. The actions of 100 nmol/L and 300 nmol/L substance P are shown in A and B, respectively. In each, the upper section illustrates an original record while the lower shows an analysis of the instantaneous frequency of the transients.

Interestingly, CGRP relaxes vascular smooth muscle via a G-protein-coupled mechanism, resulting in a rise in intracellular cAMP. This inhibition also shows a desensitization on repeated application of CGRP, similar to that seen here [32]. It is known that a rise in cAMP produces a similar reduction in frequency and amplitude of the phasic activity [33]. Therefore, perhaps the cellular mechanisms activated by CGRP resulting in the reduced frequency and amplitude of the phasic activity involve intracellular cAMP.
There are sensory nerves containing substance P and CGRP within the urothelium and in the suburothelial layers [17–19]. However, no efferent function has been detected or considered for these fibres. The blood vessels in the suburothelial layer are associated with fibres containing CGRP and substance P. The substance P fibres appear to target the endothelial layer, while the CGRP fibres are associated with the vascular smooth muscle [28]. This innervation implies that it is involved in the regulation of blood flow. Therefore, such an arrangement could represent a local axonal reflex involved in the regulation of blood flow in the bladder. In support of this there are data showing that increases in bladder volume result in a reduction in vascular resistance and consequently blood flow [34]. Thus, as in the skin, such a local reflex could be involved in the local regulation of blood flow in the bladder wall.

Sensory fibres are also found in association with the intramural ganglia in the guinea pig and human. These fibres are particularly associated with nerve-cell bodies positive for NADPH-diaphorase and nitric oxide synthase [18,19]. This close arrangement was interpreted to suggest that nitric oxide within the ganglia could influence the afferent firing in the sensory nerves [19]. The physiological significance of this idea was not developed. Thus, it is clear that there are no integrated ideas or concepts that can account for most of the efferent functions of the sensory fibres in the bladder; this represents a major gap in basic understanding.

The present data suggest a specific site of influence of the efferent component of sensory collaterals; the mechanisms generating phasic activity. It has been argued that phasic activity and the local stretches which it generates are an integral part of a motor/sensory system which receives excitatory and inhibitory influences from different elements in the bladder wall [9,13]. That phasic activity can be increased and decreased suggests that the sensory outflow can be modulated. The present results show an input from the sensory fibres in the bladder wall to the phasic mechanism. In this way information about the bladder wall (stretch, deformation, paracrine signals in the urothelium, α,β-methylene ATP and nitric oxide, chemical environment of the suburothelial space and local inflammatory signals, inter alia) could contribute to
phasic activity and sensation. The possible integration of such diverse inputs suggests a considerable degree of peripheral processing of sensory information within the bladder wall.

The cells responsible for generating phasic activity are unknown but the point of contact of the sensory axon collaterals may be helpful to identify the origins of the phasic mechanism. It has been suggested that the intramural ganglia could be a site for integrating different inputs and that the resulting ganglionic output could coordinate the waves of phasic activity [4,5]. That the intramural ganglia receive input from CGRP and substance P sensory fibres [17–19] supports this possibility. The intramural ganglia also receive inputs from other types of nerve fibre (vasoactive intestinal polypeptide, encephalin, neuropeptide Y and galanin) [18,19]. Thus, these inputs may also contribute to regulating phasic activity. In this way the intramural ganglia form a local network capable of integrating inputs and coordinating output.

Analogue of ATP and substance P appear to modulate phasic activity at doses much lower than those needed to activate directly the bladder smooth muscle [10]. This suggests that the physiological role of these agents is modulatory and indirect, acting via the mechanisms generating phasic activity [9]. The present proposal that substance P may act on intramural ganglionic cells would fit with this concept. Intramural ganglionic cells have been shown to respond to exogenous ATP [35] and may be the site of action of this ATP analogue. Alternatively, the actions of the ATP analogue on phasic activity may be more complex. If ATP were to act on the sensory nerves to induce firing, this could cause the release of substance P and CGRP, which would then have their respective actions.

The present data and the work cited are summarized in Fig. 7. The sensory fibres with their cell bodies in the dorsal root ganglia contain substance P and CGRP. Some of these fibres in the suburothelial layer respond to nitric oxide and to ATP, thereby influencing afferent discharge. The present data suggest that collateral axons remain in the bladder wall and innervate the mechanism that initiates and modulates the phasic activity (pacemaker mechanism). The release of substance P and CGRP modulates the phasic activity. The integrated output of the pacemaker mechanism is then distributed throughout the bladder wall by a network of cells, resulting in coordinated contractions involving waves and local stretches. It is also likely that the pacemaker mechanism receives inputs from cholinergic and adrenergic mechanisms [5,9–11]. Also, the detrusor receives innervation from postganglionic parasympathetic cholinergic nerves that appear to be different from those involved with the phasic mechanism [5].

Applying substance P results in an excitation of the phasic mechanism; immediately on removing substance P there was a period of inhibition whereby the amplitude and frequency of the phasic activity was reduced. This is in contrast to the actions of applied CGRP, where there was inhibition, but on wash-out there was a transient excitation. The mechanisms underlying these changes are unknown; it is possible that substance P might act on CGRP fibres to release CGRP, and thus substance P excitation would generate an inhibitory component. The converse could be true for CGRP fibres, with CGRP releasing substance P. Alternatively, there may be elements within the local network of intramural ganglia which could generate these biphasic effects.

The present data suggest the operation of a basic physiological mechanism in the bladder wall; this system may be important in modulating sensory discharge from the bladder wall and consequently the perception of bladder volume. Clinically, the major problems encountered involve bladder overactivity, heightened sensory urge and incontinence. The underlying causes of these clinical complications are unknown. The mechanisms generating phasic noncicatricial activity, the mechanisms which modulate it and the sensory systems it affects may become altered, and so contribute to overactivity and urge. The presence of a local reflex involving the effector collaterals of sensory axons may be a further site where alterations to function may contribute to the overall pathological changes. For example, increased excitatory inputs to the pacemaker mechanism from sensory afferents would augment phasic activity and so produce excessive sensation and thus urge. Exploring such concepts should generate further insights into these basic but important clinical problems.

CONFLICT OF INTEREST

None declared.

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Correspondence: James I. Gillespie, The Urophysiology Research Group, School of Surgical and Reproductive Sciences, The Medical School, The University, Newcastle upon Tyne, NE2 4HH, UK. e-mail: j.i.gillespie@ncl.ac.uk

Abbreviations: IVP, intravesical pressure; CGRP, calcitonin gene-related peptide.
Regional differences in responses of rabbit detrusor to electrical and adrenergic stimulation: influence of outlet obstruction

SETH A. CAPELLO, ERIC CHIEH-LUNG CHOU* and PENELope A. LONGHURST†

Division of Urology, Albany Medical College, Albany, New York, *Department of Urology, China Medical College Hospital, Taichung, Taiwan, and †Department of Basic and Pharmaceutical Sciences, Albany College of Pharmacy, Albany, New York, USA

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OBJECTIVE

To examine regional responses of control and obstructed rabbit detrusor strips to electrical and adrenergic stimulation, and determine whether outlet obstruction causes regional variations in blood flow throughout the detrusor, as the detrusor smooth muscle of the bladder body has previously been considered homogeneous in its pharmacological properties.

MATERIALS AND METHODS

Fourteen adult male New Zealand White rabbits (Millbrook Breeding Laboratories, Amherst, Massachusetts; 3.0–3.5 kg) had their bladder outlet partly obstructed, and were compared with 10 unoperated control rabbits. Blood flow was measured with the bladder empty and at capacity, using fluorescent microspheres. Paired dorsal and ventral strips were harvested from the midline equatorial detrusor and electrically and adrenergically stimulated.

RESULTS

Obstructed rabbits had significantly higher bladder capacities and bladder weights than control rabbits. Dorsal strips from both control and obstructed rabbits contracted in response to noradrenaline, whereas ventral strips relaxed. The addition of prazosin, a nonselective α1-adrenergic-receptor blocker, completely blocked the contraction in dorsal strips, but had no effect on responses of ventral strips. There was also a regional difference in response to electrical stimulation, with ventral strips generating significantly more tension than dorsal strips in both control and obstructed rabbits. There were no regional differences in detrusor blood flow. Obstruction resulted in significantly lower responses to all forms of stimulation, and significantly less blood flow throughout the detrusor.

CONCLUSION

There are regional differences in adrenergic receptor function and response to electrical-field stimulation throughout control and obstructed rabbit detrusor, a region that was previously thought to be functionally homogeneous. These differences must be recognized and acknowledged to obtain accurate and reproducible data from in vitro studies of the bladder.

KEYWORDS

α-adrenergic, obstruction, detrusor, regional, blood flow, rabbit

INTRODUCTION

Partial BOO, e.g. as in BPH, is a significant cause of morbidity in the form of detrusor instability and LUTS. Previous studies in dogs and humans showed that BOO leads to a change in the response of detrusor muscle to adrenergic stimulation from the normal β-adrenergic receptor [AR]-mediated relaxation, to an α-AR-mediated contraction [1,2]. It was suggested that changes in adrenergic innervation or AR distribution within the detrusor may lead to detrusor instability and potentially correlate with LUTS after BOO in men with BPH [2–4].

Until recently, the detrusor smooth muscle of the bladder body was thought to be homogeneous in its physiological and pharmacological properties. However, work by Schnöder et al. [5] in obstructed rabbits showed differential growth of the dome of the bladder relative to the rest of the body, and that ventral detrusor strips generated greater tension when stimulated with electrical impulses than did dorsal detrusor strips. This was the first study to provide evidence that the detrusor is heterogeneous for physiological responses to electrical-field stimulation (EFS).

Thus we determined whether there were also regional differences in the functional responses of obstructed rabbit detrusor to adrenergic stimulation. In addition, we investigated whether variations in regional blood flow could explain differences in the responsiveness of ventral and dorsal detrusor from obstructed rabbits to EFS.

MATERIALS AND METHODS

Fourteen adult male New Zealand White rabbits (Millbrook Breeding Laboratories, Amherst, Massachusetts; 3.0–3.5 kg) had their bladder outlet partly obstructed, and were compared with 10 age- and sex-matched control rabbits that had no surgery. In previous studies we found that sham surgery did not alter rabbit bladder weights [5] or the response of rat bladder strips to adrenergic stimulation [6], and thus a sham-operated group was not included. All rabbits had cystometry and their blood flow measured after 2 weeks of obstruction.

Partial BOO was created as described previously [5,7,8]; briefly, an 8 F urethral catheter was inserted, a 2-0 silk ligature tied around the bladder neck, and the catheter...
removed. All obstructions were created by the same surgeon (S.C.) using sterile technique.

For cystometry, rabbits were anaesthetized with intravenous ketamine (37.5 mg/kg) and xylazine (5 mg/kg), the bladder drained with an 8 F urethral catheter, and the volume of urine recorded ($V_{\text{mict}}$). Obstructing ligatures were removed before starting cystometry. The bladder was filled with warmed saline at 1.6 mL/min and the intravesical pressure recorded via the urethral catheter on a 7D polygraph (Grass Instruments, Quincy, MA). Bladder filling was continued until micturition; the time to micturition was recorded and the voided volume ($V_{\text{mict}}$) calculated.

Bladder blood flow was measured with the bladder empty and at capacity using different-coloured fluorescent microspheres, as described previously [7–10]. Briefly, microspheres are injected into the arterial system in the region of the aortic outflow tract. The spheres become mixed in the system in the region of the aortic outflow. The spheres (5 µm diameter) become lodged in capillaries in the bladder and other organs. At the end of the study, tissue is analysed by chemical digestion and flow cytometry, to measure the number of microspheres per unit of tissue. The amount of blood flow per unit tissue can then be calculated. Different-coloured microspheres were used to measure blood flow first with the bladder empty and then at capacity.

The right carotid artery was catheterized with PE190 tubing (outside diameter 1.70 mm) to monitor blood pressure and infused microspheres, and the right femoral artery with PE90 tubing (1.27 mm) for reference blood withdrawal. The first blood-flow measurement was taken with an 8 F urethral catheter in place and the bladder empty for at least 10 min [9]; $V_{\text{mict}}$ was determined by cystometry. A penile ligature was placed, the bladder was filled to $V_{\text{mict}}$, and the second blood-flow measurement, using different coloured microspheres, taken 10 min later.

The rabbit was killed and the bladder removed and weighed. The bladder was distended with Krebs solution at 2.5 mL/g of bladder [11], the dome-ureter distance recorded, and strip locations marked (Fig. 1). Urothelium-denuded strips for blood-flow analyses were taken from the dorsal midline, ventral midline, dorsal-lateral, and ventral-lateral detrusor locations. The spleen was used as a reference tissue. The numbers of microspheres/g of tissue were analysed by Interactive Medical Technologies (Irvine, California).

For in vitro functional studies, paired full-thickness dorsal and ventral detrusor strips (1 cm x 2 mm) were marked and cut, starting 2.0 cm inferior to the dome (1.0 cm if the dome-ureter distance was <4.0 cm; Fig. 1). Strips were suspended in organ baths containing modified Krebs-Henseleit buffer at 37 °C [5]. They were connected to FT03 (Grass Instruments) force transducers with 2-0 silk ligatures, and tension recorded on the 7D polygraph. Strips were stretched to 2 g tension and allowed 15 min to equilibrate; the tension was then readjusted to 2 g at 15 min before starting stimulation.

For adrenergic stimulation, one dorsal and one ventral detrusor strip were pre-contracted with KCl (40 mmol/L) and $\text{CaCl}_2$ (4 mmol/L) for 20 min [6,12]. The extra calcium was included to promote the formation of a stable plateau contraction. Noradrenaline was then added to the baths cumulatively (0.01–100 µmol/L). After the highest concentration of noradrenaline had been added, strips were washed until baseline tension was achieved. Strips were then incubated with prazosin (10 µmol/L) for 30 min, again pre-contracted, and another concentration–response curve generated.

The remaining dorsal and ventral detrusor strips were exposed to EFS using an S88 [Grass Instruments] stimulator, using pulses with an amplitude of 100 V and duration of 1 ms. Strips were stimulated for 15 s every 3 min, and then incubated with either Nω-Nitro-L-arginine methyl ester (L-NAME, 10 µmol/L) or suramin (100 µmol/L) for 30 min, and a second curve produced. Finally, strips were incubated with tetrodotoxin (1 µmol/L) before generating a third curve. Acetylcholine, indomethacin, noradrenaline, L-NAME, prazosin hydrochloride, suramin and tetrodotoxin were obtained from Sigma-Aldrich Co., St. Louis, MO, USA.

Data are expressed as the mean (SEM); contractile responses were corrected for differences in strip size using the calculated cross-sectional area, and relaxation data were normalized relative to the contractile response to KCl before adding the relaxant agonist and the maximum relaxation after washing [6]. The geometric mean $E_{\text{C}}$ (the concentration of noradrenaline producing half maximal relaxation) and $E_{\text{Fe}}$ (the frequency producing a half-maximal response) were obtained by nonlinear regression analysis. Groups were compared using Student’s $t$-test or ANOVA, followed by Bonferroni analysis, as appropriate, in all
cases with \( P \leq 0.05 \) considered to indicate statistical significance.

**RESULTS**

One obstructed rabbit died during the induction of anaesthesia and was not included in the data for cystometry or blood flow, but was included in strip studies. Blood flow data could not be obtained from one control and one obstructed rabbit because of technical difficulties with microsphere infusion.

Obstructed rabbits had a significantly higher \( V_{\text{rest}} \) when catheterized before starting cystometry than controls, and a significantly higher \( V_{\text{rest}} \) (Table 1). Bladder weights and dome-to-ureter distances were significantly greater in obstructed rabbits than in controls (Table 1).

There were no significant differences in the force developed in response to KCl between dorsal or ventral strips from control or obstructed rabbits, with values for control dorsal of 0.77 (0.10), control ventral of 0.74 (0.11), obstructed dorsal of 0.79 (0.11) and obstructed ventral of 0.47 (0.07) g/mm².

Ventral strips from control rabbits relaxed in response to noradrenaline (Fig. 2); this relaxation response was unchanged after incubating with prazosin, a nonselective \( \alpha \)-AR antagonist (Table 1). In contrast, dorsal strips from control rabbits had a strong contractile response to noradrenaline. The response of the dorsal strips was significantly different from that of the ventral strips for noradrenaline concentrations of \( \geq 0.3 \) μmol/L. The contractile response was blocked completely by prazosin.

Ventral strips from obstructed rabbits also relaxed in response to noradrenaline, but the magnitude of the response was significantly less than that of control strips at all concentrations of noradrenaline, and was unchanged by incubation with prazosin (Fig. 2). As in controls, dorsal strips from obstructed rabbits contracted in response to higher concentrations of noradrenaline, but the response was significantly smaller (Fig. 2). In both groups of rabbits, significantly more dorsal strips than ventral strips failed to relax by at least half in response to noradrenaline (Table 1). Incubation with prazosin had no significant effects on the sensitivity of ventral strips to noradrenaline (Table 1). However, ventral strips from obstructed rabbits were significantly less sensitive than dorsal strips from control rabbits (Fig. 2).

In control rabbits, ventral strips generated significantly more force than dorsal strips for EFS frequencies of \( \geq 8 \) Hz (Fig. 3). Similarly, in obstructed rabbits, ventral strips generated significantly more force than dorsal strips at all frequencies of EFS. Both ventral and dorsal strips from obstructed rabbits developed significantly less force in response to EFS than corresponding strips from controls (Fig. 3).

Dorsal strips from obstructed bladders were significantly less sensitive to EFS than dorsal

### TABLE 1 Cystometric properties of control and obstructed rabbits, and the relative sensitivity to noradrenaline

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Obstructed</th>
</tr>
</thead>
<tbody>
<tr>
<td>( N )</td>
<td>10</td>
<td>13–14</td>
</tr>
<tr>
<td>( V_{\text{max}} ), mL</td>
<td>11.7 (2.3, 4.0–26.0)</td>
<td>65.3 (12.9, 18.0–187.0)*</td>
</tr>
<tr>
<td>( V_{\text{max}} ), mL</td>
<td>17.0 (2.4, 8.5–30.8)</td>
<td>43.9 (11.8, 5.9–129.0)*</td>
</tr>
<tr>
<td>Bladder, g</td>
<td>2.48 (0.13, 1.83–3.06)</td>
<td>10.37 (0.94, 4.48–18.13)*</td>
</tr>
<tr>
<td>Dome–ureter, cm</td>
<td>3.9 (0.1, 3.5–4.8)</td>
<td>6.3 (0.2, 5.2–7.6)*</td>
</tr>
</tbody>
</table>

Relative sensitivity to noradrenaline:

<table>
<thead>
<tr>
<th></th>
<th>No. of responders†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventral</td>
<td>8</td>
</tr>
<tr>
<td>Ventral + prazosin</td>
<td>10</td>
</tr>
<tr>
<td>Dorsal</td>
<td>0</td>
</tr>
<tr>
<td>Dorsal + prazosin</td>
<td>8</td>
</tr>
</tbody>
</table>

Mean (95% CI) \( \log \) pD

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Obstructed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventral</td>
<td>6.11 (0.48)</td>
<td>5.26 (0.53)*</td>
</tr>
<tr>
<td>Ventral + prazosin</td>
<td>6.24 (0.39)</td>
<td>5.13 (0.55)*</td>
</tr>
<tr>
<td>Dorsal</td>
<td>0</td>
<td>1/14</td>
</tr>
<tr>
<td>Dorsal + prazosin</td>
<td>8</td>
<td>4/14</td>
</tr>
</tbody>
</table>

* \( P < 0.05 \) vs controls; † number of bladders with strips in which noradrenaline relaxed KCl-pre-contracted strips by at least half responders/total bladders evaluated; ‡ mean pD

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Frequency, Hz

groups based on bladder mass, i.e. obstructed rabbits were divided into two functional responses and blood flow, the To test the effects of bladder mass on blood flow to the spleen of obstructed rabbits, and there were no differences in in obstructed rabbits when the bladder was empty and at capacity. Splenic blood flow to the spleen of control rabbits at However, there was a significant increase in of control or obstructed bladders (Fig. 5). There were no significant effects on blood flow to any region of control or obstructed bladders (Fig. 5). However, there was a significant increase in blood flow to the spleen of control rabbits at full bladder capacity than when empty. Bladders from obstructed rabbits had significantly less blood flow/g of tissue to all regions than controls, both when the bladder was empty and at capacity. Splenic blood flow in obstructed rabbits when the bladder was empty did not differ from that in control rabbits, and there were no differences in blood flow to the spleen of obstructed rabbits at capacity.

To test the effects of bladder mass on functional responses and blood flow, the obstructed rabbits were divided into two groups based on bladder mass, i.e. <10 g and >10 g, with means of 7.76 (0.69) and 12.99 (1.02) g (seven rabbits each), respectively. There were no significant differences in responses to EFS or noradrenaline, or in blood flow, between the groups; the data were similar to those obtained when all the obstructed rabbits were combined as a single group (data not shown). Thus, all the obstructed rabbits were considered to have bladders that were uncompensated, based on the criteria of a significantly lower response to EFS and adrenergic stimulation [6].

DISCUSSION

There were significant regional differences in the responses of the rabbit bladder to adrenergic stimulation. Dorsal detrusor strips contracted in response to noradrenaline and ventral strips relaxed. These differences persisted even after partial BOO, although the responses of the detrusor to all forms of stimulation were greatly diminished. Furthermore, there were no differences in regional blood flow within the detrusor, but significantly less blood flow/g of tissue in obstructed detrusor than in controls.

The sympathetic nervous system is important in the bladder’s ability to store urine. Levin and Wein [13] studied AR distribution in control rabbits, using pharmacological and radioligand-binding techniques on strips taken from random areas of the bladder; they found that inhibitory β-AR predominated over excitatory α₁-AR in the detrusor. However, in this and a previous study, we examined regional responsiveness of detrusor smooth muscle to adrenergic stimulation in greater detail, finding that α₁-AR predominates over β-AR in dorsal detrusor from control rabbits [14]. Thus, dorsal rabbit detrusor strips contract in response to noradrenaline, while ventral strips respond with the expected relaxation. This suggests that there is a relatively greater density of α₁-AR than β-AR in the dorsal bladder body. This

FIG. 3. Response of ventral (red squares) and dorsal (green circles) detrusor strips from 10 control (closed) and 14 obstructed (open) rabbits to EFS. P < 0.05 vs *corresponding control strips, or † vs ventral strips from the same group of rabbits.

FIG. 4. Response of ventral (a,c) and dorsal (b,d) detrusor strips from 10 control (a,c) and 14 obstructed (b,d) rabbits to EFS in absence (red solid circle) and in the presence of L-NAME (1 μmol/L, green open circle), suramin (10 μmol/L, light-red closed square), or tetrodotoxin (1 μmol/L, light-green open square). P < 0.05 vs *corresponding control strips, † vs same strips in the absence of antagonist.
Spleen

**Explanation**

The present study confirmed that the bladder body is not homogeneous, and suggests that other aspects of bladder physiology and function may also vary with the region of the bladder examined.

We did not analyse the specific subtypes of α1-AR in this study; our recent functional receptor studies in control rabbits showed that the noradrenaline-induced contraction of the dorsal rabbit detrusor was mediated primarily by α1A-AR [14]. Hampel et al. [15] measured the expression of mRNA for α1A-AR subtypes and found that α1A-AR predominated in control rat detrusor, while the relative density of α1A-AR significantly increased after obstruction, and became the primary α1A-AR subtype in obstructed detrusor. The role of these subtypes of α1-AR in development of LUTS after BOO remains to be fully elucidated.

The present results also confirm the findings of Schröder et al. [5], that there are regional differences in responses to EFS that persist in a reduced form after obstruction. An unexpected observation by Schröder et al. was the relaxation of some of the dorsal strips from obstructed rabbits to low-frequency stimulation. In the present study, dorsal strips from four obstructed rabbits responded to low-frequency EFS with a slight relaxation or inhibition of spontaneous contraction. The addition of L-NAME (a nitric-oxide synthase inhibitor) and suramin (a P2Y receptor antagonist) caused no change in the relaxant responses, but there were too few samples for any significant conclusions (Fig. 4). Our data suggest that nonadrenergic, noncholinergic relaxant mechanisms had no major role in the response to EFS.

Differences in blood flow may be important, in that tissue ischaemia or hypoxia may be a contributing factor leading to tissue remodelling and decapsulation after obstruction. Blood flow within the rabbit bladder initially increases during the first several days after obstruction, then subsequently decreases to significantly below control levels, starting at ∼1 week after obstruction [7,8,10]. However, no one has previously investigated whether blood flow varies in different regions of detrusor. We found no significant regional differences in blood flow throughout the detrusor, either in control or obstructed rabbits. However, we showed clearly that the blood flow to the detrusor of obstructed rabbits was less overall than in controls, in agreement with previous studies [7,8,10]. Thus, the present results suggest that the need for blood flow to maintain the metabolic functions of the bladder muscle does not vary with location, but remains fairly constant throughout the detrusor, even during BOO.

That there are regional differences in response to adrenergic and EFS within detrusor is a new and exciting finding. This indicates that the detrusor is not a homogeneous region, as was once thought. The detrusor is a distinct entity from the bladder neck and trigone with respect to AR density and distribution [13,16]. However, it is now clear that the rabbit dorsal detrusor is distinctly different from ventral detrusor in adrenergic responsiveness. Also intriguing is that these regional differences exist in control animals and not just after obstruction.

The implications of the present findings are very significant; much of the understanding of the pharmacology of the bladder has been derived from bladder-strip studies. Although the techniques remain valid, the present findings and those of others [5,14] suggest that the results may vary considerably with the location from which the strips were taken. The results of previous studies must be questioned, based on these findings. Furthermore, future studies should be designed to test for regional differences and should specify clearly from where the strips were taken.

**ACKNOWLEDGEMENTS**

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**CONFLICT OF INTEREST**

None declared. Source of funding: NIH and Albany Medical College.

**REFERENCES**


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**FIG. 5. Regional blood flow in ventral and dorsal detrusor strips from nine control (a) and 12 obstructed (b) rabbits, empty (red) or at capacity (green); P < 0.05 vs *corresponding control strips or t vs empty.**


Increased blood flow after catheterization and drainage in the chronically obstructed rabbit urinary bladder. Urology 2001; 58: 295–300


Correspondence: Seth A. Capello, Albany Medical Center, South Clinical Campus, 23 Hackett Boulevard, Mail Code 208, Albany, NY 12208, USA.
e-mail: capels@juno.com

Abbreviations: AR, adrenergic receptor; EC50, concentration of noradrenaline producing half maximal relaxation; EF50, frequency producing half maximal response; L-NAME, Nω-nitro-L-arginine methylester; Vinit, volume of urine in the bladder at the time of catheterization; Vmict, volume of saline in the bladder at time of micturition or leak (bladder capacity).
Genomic research and prostate cancer: what does it offer us?

LOREENA A. JOHNSON and WILLIAM J. LYNCH
Department of Urology, St George Medical Centre, Sydney, Australia
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KEYWORDS
prostate cancer, gene profiling, oncogenesis

INTRODUCTION
What new diagnostic and prognostic techniques have been added to the clinical repertoire for prostate cancer as a result of molecular studies? Essentially, none. The main technique for diagnostics in the clinic is still histochemistry and immunohistochemistry, with the most recent being PSA in 1990s. Such techniques are quick, economical, require minimally invasive procedures and support a vast array of data. Certainly there is room for improvement; a pathologist can only interpret what is available in the biopsy, and PSA is not a tumour marker in and of itself. What then are the alternative molecular techniques being offered and what data do they provide the clinician?

In the research laboratory in situ hybridization (ISH) and fluorescentISH (FISH), semiquantitative real-time PCR, comparative genomic hybridization (CGH), assorted types of microarrays and their associated technologies are the norm. With such tools every aspect of the genomic and proteomic profile during prostate cancer oncogenesis can be examined, and they are frequently heralded in the medical and biotechnology literature as the next generation of diagnostic and prognostic tools. They have been under development for some time now, yet there is little indication that they have entered mainstream clinical practice or are likely to in the near future.

For today's clinician there is little incentive to invest in such techniques and associated technologies. They are significantly more expensive per patient sample, require specialized personnel and equipment, and take as long, if not longer, than current standards for data that have little apparent clinical application. Regardless of the pros and cons, public awareness of new technologies via education campaigns has placed pressure on the clinician to remain abreast of such technology. This overview attempts to examine the data from a cross-section of molecular studies and interpret the results from a clinical perspective.

ISSUES WITHIN FUNDAMENTAL RESEARCH
The disease presents two fundamental research challenges. First, that of multiple foci and second, genetic heterogeneity between different primary foci in the same prostate. Without isolating and identifying common genetic elements, it is difficult to propose realistic mechanistic models, and without such models it is impossible to propose changes to present treatment regimens. Thus, the main thrust of basic molecular research has been and continues to be the hunt for common genetic and proteomic elements. Given the size and complexity of the human genome, the search until recently has been relatively slow. Now with the advent of the next-generation hybridization and PCR technologies the speed at which the genome and its products can be explored has dramatically increased.

Unfortunately the literature assumes prior knowledge of the technical issues involved with each technique. While an in-depth technical discussion is beyond the constraints of this review, we define and discuss some of the more common issues on the associated web site (www.sgu.com.au). This includes the particularly frustrating issue of definitions, jargon and incorrect and overlapping use of acronyms. For example, ‘microarray’ or ‘gene chips’ are often used ubiquitously and interchangeably to indicate such a diverse range of techniques as cDNA microarrays, oligonucleotide microarrays, fluid microarrays (for protein arrays) and tissue microarrays. RT-PCR has been used to indicate both real-time PCR and reverse-transcriptase PCR.

Other technical aspects discussed include the choice of control samples, number and selection of primer/probe for hybridization techniques (e.g. CGH, PCR), signal enhancement and analysis, and microarray template varieties and selection.

Another area of assumed knowledge is patient sample collection and selection. The time between specimen retrieval and processing (fresh [1] vs autopsy specimens [2]) and sample processing (paraffin-embedded vs frozen [3,4]), are known to affect the quality of patient samples, yet are seldom addressed. In selecting appropriate patients, small numbers are the rule rather than the exception. Obtaining large samples requires longer enrolment periods, collaboration, or the most common option, increasing experimental variables, e.g. the range of grade or stage. The result is generally that there are too few patients in any one category to be statistically interesting, let alone relevant.

EXPERIMENTAL DATA OVERVIEW
Genomics and proteomics are still in their infancy and much of the data generated has yet to be analysed, interpreted and placed within context. We have tabulated in vivo results from a cross-section of published genomic DNA and RNA prostate cancer studies. Figure 1 provides a summary of the chromosomal locations (with associated references on the website).

Table 1 [1,2,5–17] summarizes cross-sectional data relating to chromosome 8; it includes (where available) the clinical stage of samples, percentage of patient samples affected, suggested gene/product of interest and the possible role in oncogenesis, as well as the techniques used to obtain the data. This table is an extract of a master table detailing data available on the rest of the human genome (available on the website).

A brief glance confirms the apparent heterogeneity between histological grades.
FIG. 1. Continued

Key:
Numbers correspond to the bibliographic reference and colours as follow:
- Red: denotes deletion/dow regulation mutation
- Green: denotes insertion/up regulation mutation
- Black: indicated change but not type of mutation
- Blue: change due to experimental parameters.
and the site and/or type of mutation. For example, insertion-type mutations at chromosome 17q21.1 appear in samples from patients with both localized disease and distant metastases, as compared to normal and BPH controls. Specific regions aside, deletion mutations in the genomic DNA appear 1.5–5 times more often than insertional type mutations [5–8]. Also obvious is the apparent lack of a unique molecular event, universal to all patients with prostate cancer, during early oncogenesis. For example, a change in gene expression of prostate-specific membrane antigen (11p11.2) in all the patients reported by Stamey et al. [21] (Gleason grade 4/5) is not reflected in similar studies [6,7,22]. As above, this may be an artefact of the broader range of patients selected, but studies using alternative techniques targeting changes in expression present a similar profile.

Late prostate oncogenesis, the clinical equivalence of which encompasses metastatic disease, appears to have several frequently occurring genomic alterations. However, several are also common to late-stage

---

**TABLE 1** A summary of chromosome 8

<table>
<thead>
<tr>
<th>Locus</th>
<th>Mutation</th>
<th>Possible gene of interest</th>
<th>Possible role in prostate cancer</th>
<th>Grade</th>
<th>Technique</th>
<th>% of sample</th>
<th>Ref</th>
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<tbody>
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<td>8p</td>
<td>deletion</td>
<td>T1-4,Nx,Mx,0,1 vs norm</td>
<td>T1NxMx</td>
<td>CGH &amp; FISH</td>
<td>73</td>
<td>[19]</td>
<td></td>
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<tr>
<td></td>
<td>deletion</td>
<td>T1-4,Nx,Mx</td>
<td>T1NxMx</td>
<td>CGH</td>
<td>10.4</td>
<td>[14]</td>
<td></td>
</tr>
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<td>deletion</td>
<td>4-5</td>
<td>T1-4NxMx</td>
<td>CGH</td>
<td>22</td>
<td>[1]</td>
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<tr>
<td></td>
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<td>GS 5-10</td>
<td>GS 5-9</td>
<td>MSI</td>
<td>69</td>
<td>[6]</td>
<td></td>
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<tr>
<td></td>
<td>deletion</td>
<td>GS 5-9, T2+3N0/M0</td>
<td>TXN+M0</td>
<td>CGH, FISH, PCR</td>
<td>[2]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>deletion</td>
<td>N/A, 17 malignant tumours</td>
<td>1 benign</td>
<td></td>
<td></td>
<td></td>
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<td>deletion</td>
<td>Contains NKX3.1 gene prostate specific</td>
<td>Possible TSG</td>
<td>T2N0</td>
<td>CGH</td>
<td>Common [15]</td>
<td></td>
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<td>N33</td>
<td>Possible TSG</td>
<td>rare</td>
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<td>T1NxMx</td>
<td>CGH</td>
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<td></td>
<td>deletion</td>
<td>human acid ceramidase gene</td>
<td>Promotes apoptosis</td>
<td>GS 5-7, BPH, cell lines, norm</td>
<td>SB, NB RT-PCR</td>
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<td>Lipoprotein lipase</td>
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<td>GS 5-10</td>
<td>CGH</td>
<td>[19]</td>
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<td>c-MYC</td>
<td>Prostate cancer, BPH</td>
<td>FISH TMA</td>
<td>&lt;11</td>
<td>[8]</td>
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<td>Oncogene</td>
<td>FISH TMA</td>
<td>&lt;11</td>
<td>[8]</td>
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<td>[8]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>insertion</td>
<td>c-MYC</td>
<td>Oncogene</td>
<td>FISH TMA</td>
<td>&lt;11</td>
<td>[8]</td>
<td></td>
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<tr>
<td></td>
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<td>Oncogene</td>
<td>FISH TMA</td>
<td>&lt;11</td>
<td>[8]</td>
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<tr>
<td></td>
<td>insertion</td>
<td>c-MYC</td>
<td>Oncogene</td>
<td>FISH TMA</td>
<td>&lt;11</td>
<td>[8]</td>
<td></td>
</tr>
<tr>
<td>8q24</td>
<td>insertion</td>
<td>Contains c-MYC region of cell proliferation diff. and apoptosis</td>
<td>T1-4,Nx,Mx,0,1 vs norm</td>
<td>CGH &amp; FISH</td>
<td>10</td>
<td>[19]</td>
<td></td>
</tr>
<tr>
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<td>Oncogene</td>
<td>FISH TMA</td>
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<td>[8]</td>
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<td>Oncogene</td>
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<td>&lt;11</td>
<td>[8]</td>
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<td>FISH TMA</td>
<td>&lt;11</td>
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<td>FISH TMA</td>
<td>&lt;11</td>
<td>[8]</td>
<td></td>
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<tr>
<td>8q24.1</td>
<td>AE</td>
<td>MYC proto-oncogene</td>
<td>Prostate cancer, BPH</td>
<td>GC</td>
<td>[5]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8q24.12−q24.13</td>
<td>AE</td>
<td>v-myc avian myelocytomatosis viral oncogene homologue</td>
<td>GS 5-10, BPH</td>
<td>GC</td>
<td>[7]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
oncogenesis of other unrelated cancer types. For example, down-regulation of the tumour suppressor gene protein tyrosine phosphatase (PTEN, 10q23) is also common to brain, breast and ovarian cancer [8–10,23]. The indication is that by late oncogenesis many of the alterations are similar to those in other cancers. This raises an interesting clinical issue as to whether it is reasonable to expect advanced prostate cancer to respond to treatment regimens in a similar manner to other cancers in late stages. Pharmaceutical and biotechnology companies have certainly taken this possibility seriously, as evidenced by several clinical oncology trials.

Comparing techniques, it is notable that most of the DNA studies (based on CGH, FISH, microsatellite analysis and PCR) are in agreement with respect to mutational types and sites across the genome. For example, 8p appears to be affected almost exclusively by insertion mutations, whilst 8p seems particularly susceptible to deletions (Fig. 1). The exceptions in mutational type which occur include conflict between studies [e.g. [6] vs [11] at 2q33] and conflict between significant numbers of the same sample population ([11], 13q arm). Some exceptions can be attributed to differences in experimental variables, including selection of patient samples and differences in techniques. Others may be true data, reflecting the uniqueness of individual genomic profiles. At present it is not always possible to distinguish the difference.

As yet, transcriptional profile studies on patient samples using microarray technology are relatively rare [1,2,4,6,7,12,22]. Microarray parameters are often chosen based on data provided by DNA studies, the inference being that these regions will be of the most immediate interest to prostate oncogenesis. Direct interpretation should be approached cautiously, but a general scrutiny offers some interesting insights. For example, an area where changes noted in the DNA studies are matched by those seen in transcriptional studies, e.g. the deletion/down-regulation at 10q26 [11,21], reinforces the DNA/RNA interrelationship, where a change in the DNA is reflected by a change in the transcriptional rate. An alteration in mRNA patterns with no changes in the DNA may indicate distant transcriptional control of the gene, e.g. annexin 4 at 2p13 [1]. A change in the genomic DNA with no change in mRNA levels, e.g. retinoblastoma suppressor gene (Rb1) at 13q14 [13], initially provokes questions about experimental variables, including the issue of mistaken identity/location, distant control elements, whether an appropriate probe was included for the region, and the histological grade of the samples. Down-regulation of mRNA with an insertion mutation in the DNA region, e.g. 5q32–34 [21,24], may indicate frame-shift mutations that physically disable the transcription of the region, while deletion of code with up-regulation of transcripts, e.g. 22q13 [11,21], aside from the experimental variables like incorrect locations, may yet indicate removal of control elements and mechanisms.

Interestingly, most of ‘common’ DNA changes are not reflected by the current transcript studies (Fig. 1). For example, chromosomes 8, 10 and 16 are well documented in DNA studies as ‘hot spots’ during prostate cancer oncogenesis [3,11,14,15,18,19,21,24–26] but it is suggested that this may be artefact rather than truth. A summary of the mutagenic information from DNA and mRNA studies (Fig. 1) confirms that chromosomes 8, 10 and 16 are oncogenically active, but also indicate that chromosomes 17, 7 and 5 and several regions within chromosomes such as 13q [2,5,11,13,24,27–30] and 18q [5,11,21,28,30–32] appear equally active. Further, chromosome 8 shows relatively little change in mRNA levels (up or down) compared to the genomic DNA data. Chromosome 10q and 16 mRNA patterns are potentially better matched, but there are still significant differences. The obvious inference is that more regions of interest have yet to come to light, probably with similar penetrance to those already known.

This however is the limit of what can be confirmed with any certainty. As indicated above, DNA and mRNA studies are intimately related. Combined, they provide greater insight into the process of prostate oncogenesis than when analysed separately. Yet there is often a failure to take into account DNA heterogeneity between samples from ‘normal’ patients, particularly when selecting controls or ‘normal’ samples. ‘Notable’ differences between gene expression of normal adjacent prostate tissue of patients with prostate cancer compared with commercial pools of normal prostate tissue has been particularly noted by Dhanasekaran et al. [6]. This individual heterogeneity increases the difficulty in identifying true disease-related changes from individual idiosyncrasies. It also raises questions about the relevance of direct comparison between mRNA studies and genomic studies of unrelated patient samples, and why genomic and transcriptional (mRNA) profile studies on the same patient sets [e.g. [1,33]] are so rare. Until studies using different techniques on the same series of tightly graded patient samples are completed, it is unlikely that a realistic picture of prostate cancer oncogenesis will emerge.

There are also several non-technical issues affecting data interpretation. These include heterogeneity in data presentation, e.g. deletions at 8p22 in patient samples of Gleason score 5–9, and T1 to metastases. Several reports [e.g. [21] vs [5,7,34], have used various statistical platforms such as hierarchical clustering algorithms [6] and meta-analysis [1] to compare data from similar studies, with varying degrees of success. In this review no statistical analysis was attempted, as the differences among experimental variables of the chosen studies render this exercise fruitless.

Other concerns include data presentation; selective presentation of data is unavoidable, particularly with the data volumes generated by techniques such as microarrays. Unfortunately this means a great deal of ‘incidental’ information is also lost to the general community. The use of databases such as the National Centre for Biotechnology Information to link potential genes/gene families to an experimentally indicated chromosomal region, can also lead to confusion. The databases detail the collective research for each particular location (see the list of genes found at 8p22; Table 1). However, the list of genes provided may or may not include genes involved with prostate oncogenesis, nor is this list necessarily complete.

GENERAL ISSUES

There is a widening communication gap between the clinic, academia and industry. This is not immediately obvious, as the volume of reports published in the last 4 years is exponentially greater than that of the preceding decade. Yet this wealth of information is a major part of the problem for the clinician. Reading entire original articles outside those that are directly relevant has become almost impossible. Even the advent of
online journals and smarter search engines do little to alleviate this problem. There is little choice but to use ‘reviews’, e.g. [16,17], to supply a summary of the available information, with all the inevitable pitfalls and misinformation that this can create.

Definitions too, vary across the disciplines; e.g. early oncogenesis in the clinic is based on the appearance of symptoms such as a rising PSA level. In the laboratory, early stages of oncogenesis can be assumed as the first of the genetic abnormalities occurring in the single-cell foci. In a clinical setting this is a long way from becoming a symptomatic issue. The body has its own defences; most cells never accumulate the required changes to overcome the many defence mechanisms, such as DNA repair and apoptotic mechanisms. In the future this pre-symptomatic information will probably be essential for diagnostic tools and for preventative treatments, but in today’s clinic, such information has little practical use and can be worse than useless to the patient.

These issues highlight another fundamental gap in our understanding of prostate oncogenesis. Our knowledge of normal prostate and healthy prostate cells, their cellular interactions, life cycle and molecular status remains incomplete. For example, KLK3 [at 19q13, previously known as hK3 and clinically known as PSA] is possibly the most intensively studied of the prostate-specific proteins (refer to the master table on the website and the associated references). Yet major aspects such as the controlling mechanisms are not fully understood. It is curious then, that there appears to be little ongoing fundamental research published on the prostate. There are general problems associated with prostate research, including economics, ethical issues, physical location of the prostate and the paucity of true animal models. Alternatives such as prostate cancer cell lines, xenografts and prostate cancer tissue banks are therefore very important in prostate cancer research, as is attested by the percentage of in vitro studies. However, in vitro alternatives have their limitations, particularly when attempting to understand the ‘normal’ prostate. From a clinical perspective it is difficult to see how a ‘realistic’ interpretation of prostate oncogenesis can be made when ‘normal’ parameters of the healthy prostate have yet to be established.

It is also unfortunate that many of the older DNA techniques, e.g. CGH, FISH, and Southern blot, seem to be passing from favour. Instead, expensive high-maintenance research such as oligonucleotide and cDNA microarrays have become de rigueur to secure funding. Why? The short answer is data volume. Pharmaceutical and biotechnology companies have been able to take advantage of these mass data techniques, and by popularizing and educating the public, applied pressure on the research community to keep pace. This ostracises not only the research-orientated clinician but also many of the smaller university and hospital laboratories, for whom these techniques are simply too expensive. The result is a reduction in the pool of experience, ideas and results within the area, and a lessening of the flow and perceived worth of data provided by these older DNA/genomic techniques. A word of support then, for these less fashionable techniques. Their relevance is proven, they are within reach of the overall research community and have the advantage of providing useful information, complementary to that provided by microarray technology.

CONCLUSION

So what new insights into prostate cancer management can molecular studies provide to today’s clinician? Little or nothing, directly. However, we can surmise the following. First, there is not yet enough data to translate into anything immediately clinically useful. For example, there appears to be no clear association between gene region and stage of oncogenesis, although this may be as much a result of insufficient data from well-designed experiments than fact. Second, prostate cancer is not a simple single gene/gene family mutational disease. Different foci within the same prostate can have a different genomic profile. Further, once established and progressing, the aneuploidy nature of the later stages of oncogenesis enables increased random mutation types and numbers to occur independently of one another. This not only makes analysis of progression difficult, in clinical terms it means that the chances of a particular prostate cancer focus surviving a treatment regimen are greatly enhanced. Third, the research technology and techniques used in today’s molecular laboratory are simply not practical for the clinical environment.

Will molecular genomics and its associated technologies have a future in the clinic? Yes; its greatest potential being in the next developmental stage of patient care, i.e. affordable, customized diagnostics, treatment and prevention regimens for the individual. Every patient has a different response to a disease agent and the drugs that are used to treat them. These differences are often so minute that the same treatment regimen can be used safely in the vast majority of people, e.g. antibiotics for treating bacterial infections. The scientific community and the media have impressed upon us the overall genetic similarity of species, which is important in as much as it enables research on other individuals and other species to have relevance to us. However, the differences are still there. It is not the homology that is the future issue for medical research, it is the tiny percentage difference (i.e. heterogeneity) which dictates the response differences that will become the core around which individual treatment regimens are built. This then, is where we predict molecular genomics will come into its own in the clinical setting.

CONFLICT OF INTEREST

None declared.

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Correspondence: William J. Lynch, Department of Urology, St George Medical Centre, Sydney, Australia. e-mail: lynch@sgu.com.au

Abbreviations: (F)ISH, (fluorescent) in situ hybridization; CGH, comparative genomic hybridization.
Genetic polymorphism of glutathione S-transferase genes (GSTM1, GSTT1 and GSTP1) and susceptibility to prostate cancer in Northern India

DAYA SHANKAR LAL SRIVASTAVA, ANIL MANDHANI, BALRAJ MITTAL* and RAMA DEVI MITTAL
Departments of Urology and *Genetics, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India
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OBJECTIVE
To examine the association of glutathione S-transferase (GST) gene polymorphisms in patients with sporadic prostate cancer, in a North Indian population, as GSTs are active in detoxifying a wide variety of endogenous or exogenous carcinogens, and genetic polymorphisms of GSTM1, GSTT1 and GSTP1 have been assessed to evaluate the relative risk of various cancers.

PATIENTS AND METHODS
We assessed 127 patients with prostate cancer and 144 age-matched controls, all from North India. The GSTT1 and GSTM1 null genotypes were identified by multiplex polymerase chain reaction (PCR) in peripheral blood DNA samples, and GSTP1-313 A/G polymorphism was determined by PCR/restriction fragment length polymorphism.

RESULTS
There was a significant association in null alleles of the GSTM1 (odds ratio 2.239, 95% confidence interval 1.37–3.65, P = 0.001) and GSTT1 (1.891, 1.089–3.282, P = 0.026) with prostate cancer risk, and in the -313 G alleles (Val) of the GSTP1 gene (2.48, 1.51–4.08, P < 0.001). The combined analysis of these three genotypes showed a further increase in the risks of prostate cancer (7.23, 2.42–22.6, P < 0.001).

CONCLUSION
The GSTP1-313 G polymorphism, and null alleles of GSTM1 and GSTT1, are strong predisposing risk factors for sporadic prostate cancer in North India.

KEYWORDS
glutathione S-transferase polymorphism, prostate cancer, PCR-RFLP, null genotypes

INTRODUCTION
The phase II metabolizing enzymes, e.g. glutathione S-transferase (GST), N-acetyltransferase, epoxide hydroxylase and sulphotransferase, are involved in detoxifying chemical carcinogens and subsequently their role is expected to be protective [1]. Cytosolic GSTs are a family of related isozymes that catalyse the conjugation of reduced glutathione to a wide range of electrophilic substrates [2]. GSTs are generally involved in detoxification, but they are also important in activating and inactivating oxidative metabolites of carcinogenic compounds associated with causing prostate cancer [3]. Among them the most extensively studied are the GSTM1 null, the GSTP1-313 A/G substitution and the GSTT1 null polymorphism. The functional consequences of the GSTM1 and the GSTT1 null genotypes are obvious in terms of enzyme activity; no gene, no enzyme and no activity. The GSTP1-313 A/G polymorphism at the nucleotide level leads to an amino-acid variation of isoleucine/valine at codon 105 in the protein. Valine amino-acid substitution results in decreased enzyme activity [4]. GSTM1 mα class has been recognized to detoxify smoke-derived carcinogens, e.g. polycyclic aromatic hydrocarbon and aromatic amines [5,6]. Some substrates are metabolized by specific GSTs because of their capacity in overlapping substrate specificity [7,8].

Combinations of various unfavourable deletion genotypes theoretically confer an even higher risk to patients with prostate cancer. An increased frequency of GST genotypes has been associated with several malignancies [9–11]. Some studies indicate that GST polymorphisms are associated with prostate cancer [12–15], but others do not [16,17]. Although promising data from these studies are accumulating at a remarkable pace, they are still too sparse to support a role for a specific gene in the risk of prostate cancer. Recent reviews suggest that the frequencies of some polymorphisms in certain genes differ among different racial and ethnic groups [18]. Whether these genetic variants can help to explain part of the large differences in prostate cancer risk among various populations awaits further clarification.

In the present study, we determined the genotypic frequency of the GSTM1 null, GSTT1 null and the GSTP1-313 A/G polymorphism, to understand whether the GST polymorphisms are associated with the risk of sporadic prostate cancer in North India.

PATIENTS AND METHODS
The study group comprised 127 men with prostate cancer (mean age 62.5 years) and 144 controls (mean age 58.5 years). The criteria for selecting patients were based on a clinical proforma, covering medical, pathological and histopathological records from the outpatient department of the authors’ institution, from December 2001 to February 2004. The study was approved by ethical committee of the institution. Only men with histologically confirmed prostate cancer were included in the study; all had high Gleason scores (6–9) and were detected at an advanced stage because there is no structured screening programme under any health...
scheme in India. All participants were given an explanation of the nature of the study and informed consent was obtained. The ethnic origin for cases and controls were similar. The inclusion criteria for the controls were the absence of any previous history of cancer or pre-cancerous lesions, and serological tests to indicate statistical significance.

From both cases and controls, DNA was extracted and genotyped using 5 mL blood samples collected in vials containing EDTA. Genomic DNA was isolated from peripheral leukocytes by proteinase K digestion and phenol/chloroform extraction [19]. Analysis of GSTM1 and GSTT1 gene polymorphism was carried out by multiplex PCR using the method described by Abdel-Rahman et al. [20]. Genomic DNA (100–150 ng) was amplified in a total volume of 25 μL reaction mixture containing 20 pmol of each of the following primers: GSTM1; forward 5′-GAACCTCCCTGAAAAGCTAAGG-3′ and reverse 5′-TGTTGGCTCAATAATACGGTG-3′; GSTT1, forward: 5′-TTCTCTTCTGCTGCTCCACTCT-3′ and reverse 5′-TCAGGGATCATGGCGAGGA-3′. Exon 7 of the CYP1A1 gene was co-amplified and used as an internal control, using primers: forward 5′-GAACGTCCACTGCTGCTC-3′, and reverse 5′-CACTGCTGATGGAGTGTC-3′. Each set of reactions included positive and negative controls. The multiplex PCR method was used to detect the presence or absence of the GSTT1 and GSTM1 genes in the genomic DNA samples simultaneously in the same tube. The reaction mixture was subjected to initial denaturation at 94 °C for 2 min, followed by 35 cycles of 94 °C for 2 min, 59 °C for 1 min and 72 °C for 1 min. The PCR products were electrophoresed in 2% agarose gels, and visualized by ethidium bromide staining. DNA from samples positive for GSTM1 and GSTT1 genotypes yielded bands of 215 bp and 480 bp, respectively, while the internal positive control (CYP1A1) PCR product corresponded to 312 bp. The A313G polymorphism of GSTT1 was analysed using a previously described PCR-RFLP method [21]. Briefly, amplification was carried out using primers: forward 5′-ACCCAGGAGCTATGGAAGAA-3′ and reverse 5′-TAAGGGGCAAAGAACGGCCC-3′. The 176-bp amplified product was digested with Alw261 and electrophoresed in 3% agarose gel. The presence of the restriction site resulted in only two fragments (91 and 85 bp) indicating the G allele, and if there were A/G polymorphisms then there were three fragments, of 176, 91 and 85 bp.

The results were assessed statistically using a binary logistic regression model to assess differences in genotypic prevalence and association between cases and controls. Multivariate analysis, the odds ratio (OR) and its 95% CI were used to describe the strength of association, with P < 0.05 considered in all tests to indicate statistical significance.

RESULTS

Table 1 shows the frequencies of GSTM1, GSTT1 and GSTP1 alleles and genotypes by case-control status and the association of GST genotypes with prostate cancer risk. In the control samples, the frequency of GSTM1 null and GSTT1 null was 32.5% and 20.1%, respectively. The GSTP1 Ile allele was present in 57.9% in the homoygous state (Ile/Ile) while the Val allele was homoygous (Val/Val) in 34.7%; the remaining 8.9% were heterozygous (Ile/Val). Genotype distributions in controls were in agreement with the Hardy-Weinberg equilibrium.

There was a significant association of null genotypes of the GSTM1 and GSTT1, and of the heterozygote (A/G) of the GSTP1 gene, with prostate cancer risk (Table 1). The combination of the two high-risk genotype GSTM1 null and GSTT1 null or GSTP1-313

### Table 1: The distribution, as n (%), of GST genotypes in the patients with prostate cancer and controls

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Controls</th>
<th>Patients</th>
<th>P</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N patients</td>
<td>144 (63.4)</td>
<td>127 (68.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GSTM1 null</td>
<td>57 (44.9)</td>
<td>63 (50.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Null</td>
<td>70 (55.1)</td>
<td>73 (57.1)</td>
<td>0.001</td>
<td>2.24 (1.37–3.65)</td>
</tr>
<tr>
<td>GSTT1 null</td>
<td>86 (67.7)</td>
<td>88 (68.8)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Null</td>
<td>41 (32.3)</td>
<td>39 (31.2)</td>
<td>0.026</td>
<td>1.89 (1.09–3.28)</td>
</tr>
<tr>
<td>GSTP1 I/I</td>
<td>46 (36.2)</td>
<td>50 (40.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I/V</td>
<td>77 (60.6)</td>
<td>74 (58.7)</td>
<td>&lt;0.001</td>
<td>2.48 (1.51–4.08)</td>
</tr>
<tr>
<td>V/V</td>
<td>4 (3.2)</td>
<td>5 (3.9)</td>
<td>0.986</td>
<td>1.44 (0.37–5.64)</td>
</tr>
<tr>
<td>Double</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GSTM1 and GSTT1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Both</td>
<td>95 (39.6)</td>
<td>105 (45.9)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Either null</td>
<td>65 (51.2)</td>
<td>73 (57.1)</td>
<td>0.002</td>
<td>2.26 (1.34–3.83)</td>
</tr>
<tr>
<td>Both null</td>
<td>23 (18.1)</td>
<td>21 (17.4)</td>
<td>0.001</td>
<td>3.73 (1.68–8.29)</td>
</tr>
<tr>
<td>GSTM1 and GSTP1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M1 (+) &amp; P1 (I/I)</td>
<td>57 (39.6)</td>
<td>59 (28.7)</td>
<td>19 (15.0)</td>
<td>1.0</td>
</tr>
<tr>
<td>M1 (+) &amp; P1 (I/V)</td>
<td>36 (25.0)</td>
<td>34 (15.7)</td>
<td>0.001</td>
<td>3.17 (1.59–6.32)</td>
</tr>
<tr>
<td>M1 (−) &amp; P1 (I/I)</td>
<td>26 (18.1)</td>
<td>26 (11.9)</td>
<td>0.001</td>
<td>3.35 (1.59–7.02)</td>
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<tr>
<td>M1 (−) &amp; P1 (I/V)</td>
<td>41 (32.3)</td>
<td>43 (19.6)</td>
<td>&lt;0.001</td>
<td>4.92 (2.40–10.10)</td>
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<tr>
<td>GSTT1 and GSTP1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1 (+) &amp; P1 (I/I)</td>
<td>76 (32.6)</td>
<td>81 (35.7)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>T1 (+) &amp; P1 (I/V)</td>
<td>46 (32.0)</td>
<td>51 (22.2)</td>
<td>0.001</td>
<td>2.70 (1.52–4.80)</td>
</tr>
<tr>
<td>T1 (−) &amp; P1 (I/I)</td>
<td>55 (21.6)</td>
<td>56 (24.4)</td>
<td>0.026</td>
<td>2.58 (1.22–5.93)</td>
</tr>
<tr>
<td>T1 (−) &amp; P1 (I/V)</td>
<td>21 (11.3)</td>
<td>23 (10.2)</td>
<td>&lt;0.001</td>
<td>4.03 (1.85–8.79)</td>
</tr>
<tr>
<td>Triple</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M1 (-), T1 (+)/+ &amp; P1 (I/I)</td>
<td>47 (32.6)</td>
<td>48 (22.2)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>M1 (-), T1 (+)/+ &amp; P1 (I/V)</td>
<td>29 (20.1)</td>
<td>30 (13.9)</td>
<td>0.004</td>
<td>3.24 (1.44–7.29)</td>
</tr>
<tr>
<td>M1 (-), T1 (+)/+ &amp; P1 (I/V)</td>
<td>21 (14.8)</td>
<td>23 (10.2)</td>
<td>0.012</td>
<td>3.10 (1.29–7.47)</td>
</tr>
<tr>
<td>M1 (-), T1 (+)/+ &amp; P1 (I/V)</td>
<td>18 (12.5)</td>
<td>20 (9.1)</td>
<td>&lt;0.001</td>
<td>5.83 (2.49–13.63)</td>
</tr>
<tr>
<td>M1 (+)/+, T1 (-)/+ &amp; P1 (I/V)</td>
<td>10 (7.0)</td>
<td>12 (5.4)</td>
<td>0.200</td>
<td>2.17 (0.66–7.09)</td>
</tr>
<tr>
<td>M1 (+)/+, T1 (-)/+ &amp; P1 (I/V)</td>
<td>7 (4.9)</td>
<td>8 (3.6)</td>
<td>0.001</td>
<td>6.20 (2.03–18.93)</td>
</tr>
<tr>
<td>M1 (+)/+, T1 (-)/+ &amp; P1 (I/V)</td>
<td>5 (3.5)</td>
<td>6 (2.6)</td>
<td>0.003</td>
<td>6.51 (1.86–22.80)</td>
</tr>
<tr>
<td>M1 (-), T1 (-)/+ &amp; P1 (I/V)</td>
<td>7 (4.9)</td>
<td>8 (3.6)</td>
<td>&lt;0.001</td>
<td>7.23 (2.42–22.63)</td>
</tr>
<tr>
<td>M1 (-), T1 (-)/+ &amp; P1 (I/V)</td>
<td>7 (4.9)</td>
<td>8 (3.6)</td>
<td>0.001</td>
<td>7.23 (2.42–22.63)</td>
</tr>
</tbody>
</table>

I, isoleucine; V, valine.
The association of genetic polymorphisms of GSTM1, GSTT1 and GSTP1 and prostate cancer risk according to nationality

<table>
<thead>
<tr>
<th>Gene/population</th>
<th>Cases</th>
<th>Controls</th>
<th>Comparison</th>
<th>OR (95% CI)</th>
<th>Study</th>
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<tr>
<td>GSTM1</td>
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<td></td>
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<tr>
<td>North Indian</td>
<td>127</td>
<td>144</td>
<td>Null vs non-null</td>
<td>2.2 (1.37–3.65)</td>
<td>Present</td>
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<tr>
<td>American</td>
<td>276</td>
<td>499</td>
<td>Null vs non-null</td>
<td>1.0 (0.73–1.36)</td>
<td>[22]</td>
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<tr>
<td>Japanese</td>
<td>115</td>
<td>204</td>
<td>Null vs non-null</td>
<td>1.6 (0.84–2.99)</td>
<td>[13]</td>
</tr>
<tr>
<td>Danish</td>
<td>153</td>
<td>288</td>
<td>Null vs non-null</td>
<td>1.3 (0.9–1.9)</td>
<td>[16]</td>
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<tr>
<td>German</td>
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<td>Null vs non-null</td>
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<td>Austrian</td>
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<td>Non-null vs. null</td>
<td>0.86 (0.55–1.36)</td>
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<tr>
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<tr>
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<td>1.89 (1.08–3.28)</td>
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<td>1.3 (0.8–1.7)</td>
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<td>2.31 (1.17–4.59)</td>
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<td>115</td>
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<td>Null vs non-null</td>
<td>1.6 (0.84–2.99)</td>
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<td>166</td>
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<td>0.78 (0.43–1.42)</td>
<td>[12]</td>
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<tr>
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<tr>
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<td>A/A vs A/G</td>
<td>2.48 (1.51–4.08)</td>
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<td>153</td>
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<td>A/G plus G/G vs A/A</td>
<td>0.8 (0.54–1.19)</td>
<td>[16]</td>
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<tr>
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<td>91</td>
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<td>A/G plus G/G vs A/A</td>
<td>1.08 (0.66–1.77)</td>
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<td>A/A vs A/G plus G/G</td>
<td>0.85 (0.54–1.32)</td>
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<td>0.4 (0.02–3.3)</td>
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<tr>
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<td>105</td>
<td>A/A vs A/G plus G/G</td>
<td>9.31 (0.47–18.4)</td>
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</table>

DISCUSSION

The present results indicate that the null genotypes of GSTM1 and GSTT1 and the G allele of GSTP1 are associated with a higher risk for prostate cancer than in controls (Table 1). These observations concur with previous reports in a Japanese population, where there was also an increased risk of prostate cancer for the GSTM1 null genotype [13]. On the contrary, in Austrians [12], German [14] and in American [22] studies, no association with the GSTM1 null genotype was established. In the present Indian men there was also a greater risk of prostate cancer with the GSTT1 null genotype, as reported in the German study [14], but not in the American population [22], where there was a greater risk with the GSTT1 non-null genotypes. There was also a greater risk of prostate cancer associated with the GSTP1-313 A/A polymorphism in the present men; this agrees with the findings in the Japanese study, where there was a greater risk of prostate cancer with the GSTP1-313 A/A or G/G polymorphism [15]. On the contrary, there was no association in the German and Austrian population [12,14]. Therefore, it appears that the association of prostate cancer risk with null alleles of GSTM1, GSTT1 and the G allele of GSTP1 vary greatly in different populations (Table 2).

The combination of the two high-risk genotypes, GSTM1 null and GSTT1 null or GSTP1-313 A/A or G/G genotype, increased the risk four times for GSTP1 and GSTT1, and 3.7 times for the GSTM1 and GSTT1 genotypes. However, the risk was five times greater for the null allele of GSTM1 with the GSTP1 genotype than in no-risk genotypes (Table 1); when the three risk genotypes were combined the risk increased to seven times. Combined analyses of GSTM1/GSTT1 and GSTP1 loci and their significant association were also reported in the German and Japanese studies [14,15]. The present study showed a greater risk with several risk alleles of GST, and suggests that gene-gene interaction may contribute to a causal propensity for developing prostate cancer in the North Indian population.

GSTs are active in detoxifying a wide variety of potentially toxic and carcinogenic electrophiles by conjugating with glutathione, and so their role is mainly detoxification. Besides this they are also involved in the deactivation of oxidative metabolites of exogenous or endogenous carcinogenic agents (industrial chemicals, dietary compound, tobacco products, drugs and environmental carcinogens, etc.) that are probably associated with prostate cancer risk [23,24]. Because there are inactive form of the enzymes (null genotypes of GSTM1 or GSTT1 and the G allele of GSTP1) detoxification of activated carcinogen is reduced, leading to progression of cancer. Inter-individual differences in cancer susceptibility may be mediated partly through polymorphic variability in the bio-activation and detoxification of carcinogens. Moreover GSTs also modulate the induction of other enzymes and proteins important for cellular function, e.g. DNA repair [25]. Hence, GSTs are important for maintaining cellular genomic integrity and as a result, also in cancer susceptibility.

To our knowledge this is the first genetic study of prostate cancer in the Indian population, and showed that the GSTP1-313 G allele (Val), null alleles of GSTM1 and GSTT1 are strong predisposing risk factors for prostate cancer. Moreover, the combination of three GST genotypes further increase the risk of prostate cancer in the North Indian population.

ACKNOWLEDGEMENTS

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CONFLICT OF INTEREST

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Correspondence: Rama D. Mittal, Department of Urology, SGPGIMS, Raebareli Road, Lucknow-226014, India.
E-mail: rimalittal@sgpgi.ac.in, ramamittal@yahoo.com
Abbreviations: GST, glutathione S–transferase; OR, odds ratio.
Differential endostatin binding to bladder, prostate and kidney tumour vessels

ANNETTE SCHMIDT, FRANK SOMMER†, MICHAEL REINER*, THEODOR KLOTZ‡, UDO ENGELMANN†, KLAUS ADDICKS* and WILHELM BLOCH

Department of Molecular and Cellular Sport Medicine, German Sport University, *Institute I for Anatomy, and †Department of Urology, University of Cologne, and ‡Clinic of Urology, Clinic of Weiden, Germany

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INTRODUCTION

The regulation of angiogenesis for treating different diseases is becoming more significant as a promising therapeutic method. Angiogenic inhibitors are important in suppressing tumour growth and proliferation. Endostatin, a C-terminal proteolytic fragment of collagen XVIII, is one such angiogenic inhibitor [1]. The anti-angiogenic mechanism is by inhibition of endothelial cell migration and proliferation [2]. Endostatin also induces apoptosis in endothelial and tumour cells [1,3], and is thus a potent anti-tumour agent, having its effects by inhibiting vascularity and blood supply in neoplastic tissues [1,2]. Chang et al. [4] showed that endostatin binds to vessels of different sizes, specifically to their subendothelial matrix. The potent anti-angiogenic property of endostatin, together with an absence of such effects on certain blood vascular channels, raises questions about the selectivity and specificity of the binding properties of endostatin [1]. There are contradictory published data comparing results from animal and human studies of endostatin. In clinical trials endostatin had only minor effects on various tumours. For technical reasons, the effect of endostatin on kidney, prostate and other tumours could not be investigated [5,6]. In a study on murine wound healing, endostatin had a modulatory effect on angiogenesis or wound closure [7,8]. However, there was inhibition by endostatin of kidney tumour growth, and an anti-angiogenic effect in studies using mice and rats [1,9]. Whether these discrepancies are a result of the diverse binding properties of endostatin, or of a different response to endostatin by blood vessels in normal tissue as opposed to malignant tissue vessels, or even to individual endostatin responses by vessels in different kinds of tumours, remains to be defined.

Thus the aim of the present study was to analyse, describe and compare the binding properties of endostatin to blood vessels from both tumorous and benign bladder, prostate and kidney tissues.

MATERIALS AND METHODS

To use human tissue, ethical permission was obtained from the local ethics committee of the authors’ institution. The tissue specimens were obtained from patients during surgery, with the patients’ informed consent. None of
the patients had received therapy before surgery. Normal tissue from bladder, prostate and kidney was also assessed, being taken at sites remote from the tumour.

Malignant and normal bladder tissue specimens were obtained from 12 patients; eight had had a transurethral resection and four a radical cystectomy for bladder cancer (mean age 67.9 years, median 68). On final histological staging, two patients had stage pTaG1, four pT1G2, two pT1G3, three pT2G2 and one pT3G3. Prostate samples were obtained from 12 patients (mean age 69.7 years, median 70) with prostate cancer, as prostate biopsies of normal and malignant tissue before they underwent external beam radiation and brachytherapy. In this group there were three men with pT2G1, eight with pT2G2 and one with pT2G3 disease. None of these patients had received preoperative hormonal therapy, radiation or chemotherapy.

Kidney tissues (malignant and normal) were obtained from 12 patients (mean age 63.8 years, median 64), all of whom had a nephrectomy for kidney tumours. On final histological staging three patients had stage pT2G2, four pT1G2, two pT2G3 and three pT3G2 disease.

For biotinylation of endostatin and tissue labelling, tissue samples were fixed with 4% (w/v) paraformaldehyde in 0.1 mol/L PBS (pH 7.4). After 4 h of immersion fixation, tissue sections of 50–70 μm were prepared on a vibratome and washed carefully in PBS. The endostatin-biotin binding (50 ng/mL) was conducted for 12 h at 4 °C in 0.05 mol/L TBS, followed by five washing cycles in TBS. Finally, the biotin was detected with extravidin coupled to 15 nm colloidal gold (Sigma-Aldrich, Taufkirchen, Germany) in TBS containing 0.8% (w/v) BSA overnight at 4 °C. After rinsing in TBS, the incubated tissue sections were stabilized with 2% (v/v) glutaraldehyde in cacodylate buffer (100 mmol/L di-methyl arsenic acid sodium acetate, pH 7.3) and postfixed with osmium tetroxide. After ‘en bloc’ counterstaining with 1% (v/v) uranyl acetate, the samples were dehydrated with ethanol and embedded flat in epoxy resin, using propylene oxide as the inter-medium. Thin sections with a silver-grey interference were cut on an ultramicrotome and collected on 150-mesh Formvar-coated copper grids (150 bridges per 25.4 mm, Plano, Wetzlar, Germany) which were not further stained, to intercept the gold signal in the electron microscope. Also, thin sections were collected on 100 mesh (100 bridges per 25.4 mm, Plano) Formvar-coated nickel grids for a post-extravidin method. Sections were washed three times for 15 min in TBS, made permeable with 5% (v/v) HCO, blocked with 1% (w/v) powdered milk and 0.1% (v/v) Tween-20 in TBS for 30 min at room temperature, and incubated with extravidin coupled with 15 nm colloidal gold (1 : 20, Zymed Laboratories, Inc., San Francisco, CA, USA) for 2 h at room temperature. Gold staining, to detect bound, biotinylated endostatin, was stabilized with 2% (v/v) glutaraldehyde for 10 min and counterstained with uranyl acetate for 20 min. As a control, extravidin coupled with 15 nm colloidal gold was used with no incubation of biotinylated endostatin on tissue sections. The slices were evaluated using an electron microscope at 80 kV.

For immunogold labelling, immediately after excision, the biopsies were immersed in a fixative solution containing 1% (v/v)
and 0.5 mmol/L CaCl₂, glutaraldehyde, 2% (w/v) freshly prepared formaldehyde 0.2% (w/v) saturated picric acid and 0.5 mmol/L CaCl₂ in 0.1 mol/L Heps buffer (100 mmol/L Heps–Na, pH 7.2). After 1 h, samples of 3 mm were trimmed and left in the fixative for up to 24 h. With no washing step the samples were treated with 1% (w/v) tannic acid in 0.1 mol/L Heps containing 3.5% (w/v) sucrose and 0.5 mmol/L maleate buffer (100 mmol/L maleic acid). After three washing steps in Hepes/sucrose/CaCl₂, free aldehydes were quenched with 50 mmol/L NH₄Cl in the same buffer, followed by two additional buffer washes. Then specimens were transferred to 0.1 mol/L maleate buffer (100 mmol/L maleic acid anhydrite, 3.5% (w/v) sucrose and 0.5 mmol/L CaCl₂, pH 6.0) washed three times and left overnight in the refrigerator. The sections were then stained en bloc with uranyl acid, using 2% (v/v) uranyl acetate in the modified maleate buffer for 4 h, which resulted in brown staining of the samples.

After extensive washing with maleate buffer, the samples were dehydrated in series of graded ethanol followed by three changes of propylene oxide, infiltrated and embedded in Araldite Cy212 (Serva, Heidelberg, Germany), which was finally polymerized at 56 °C. All embedding steps were carried out at 4 °C on ice. Thin sections with a silver interference colour were cut on the ultramicrotome and collected on 150-mesh nickel grids (Plano).

Within 24 h after cutting, the immunoperoxidase was applied to floating grids; sections were equilibrated in 0.05 mol/L TBS for 15 min, followed by a blocking step with 1.6–3% (w/v) BSA, and incubation with the first antibody (rabbit anti-endostatin) for 2 h at room temperature in a moist chamber at 1:400 dilution in TBS containing 0.8% (w/v) BSA. After four washing steps in TBS/0.8% BSA the grids were incubated with 10 nm gold–conjugated goat–anti-rabbit antibodies (1:20, Sigma), respectively, for 60 min in TBS/0.08% BSA. After washing in two drops of TBS and two of fresh distilled water, the grids were stained with 2% (v/v) aqueous uranyl acetate for 20 min and counterstained with lead citrate for a further 7 min. As a control, sections were incubated with the secondary antibody only. The immunolabelled sections were then assessed by electron microscopy.

For the morphometric analyses, the amount of endostatin binding to vessels was recorded on randomly selected endostatin–labelled tissue sections and presented as the mean (±sd). For each patient (four slices per patient) 50 vessels were examined with a fluorescence microscope (Axioskop, Zeiss, Oberkochen, Germany) at ×400 (CY2, absorbance 552 nm and emission 565 nm; CY3, 495 nm and 516 nm). Only vessels which were stained above a clearly detectable threshold were counted. The binding intensity was evaluated by comparison of the fluorescence intensity derived from PECAM-1 and endostatin-binding staining. Binding was 'distinct' if the fluorescence intensity derived by endostatin-binding was comparable to or higher than that derived from PECAM-1 staining. If there was a recognisable but lower fluorescence intensity of staining than that with PECAM-1 the binding was 'weak'.

The results were analysed statistically using a paired t-test for all normal and tumour samples, because both were from the same patients.

RESULTS

To determine whether differences in endostatin binding were a consequence of various levels of endogenous endostatin, whereby high endogenous levels could possibly interfere with exogenous endostatin, we used western blotting and compared endostatin levels in bladder, prostate and kidney tissues and tumour. From the western blot it was clear that endogenous endostatin levels in these tissues were not variable (Fig. 1). The collagen XVIII fragment, endostatin, is 22 kDa, whereas the NC-1 fragment of collagen XVIII is 38 kDa; thus the 25 and 30 kDa fragments were presumably those of the collagen XVIII NC-1 domain, and the 47-kDa band a proteolytic fragment of collagen XVIII.

The binding pattern was assessed in cryosections of fixed and sucrose-embedded human bladder, prostate and kidney tissue with biotinylated endostatin. In bladder tumour tissue there was distinct endostatin binding in 94.2 (3.0)% of vessels of various diameters (Fig. 2A,B), while there was weak endostatin binding in only 2.0 (1.5)% of normal bladder tissue vessels (P < 0.001). In contrast to vessels in malignant bladder and prostate tissue, only 11.3 (3.9)% of vessels in malignant kidney tissue had endostatin binding (Fig. 2E,F). The endostatin binding in malignant kidney tissue had endostatin binding in 73.8 (19.5)% of vessels of various diameters (Fig. 2C,D), while there was weak endostatin binding in 94.2 (3.0)% of vessels of various diameters (Fig. 2A,B) prostate tumour vessels (Fig. 2C,D) there was distinct endostatin binding in 73.8 (19.5)% of prostate tumour vessels (Fig. 2C,D) there was less, at 1.7 (1.7)% in normal prostate vessels. In contrast to vessels in malignant bladder and prostate tissue, only 11.3 (3.9)% of vessels in malignant kidney tissue had endostatin binding (Fig. 2E,F). The endostatin binding in vessels in normal kidney tissue was also less, at 1.5 (1.7)% (P < 0.001). Control experiments using no biotinylated endostatin had no fluorescence signal for any of the tissues (data not shown). Pre-incubation with a 100-fold higher concentration of endostatin prevented the binding of biotinylated endostatin. There was no variability in endostatin binding for the different tumour stages of bladder, prostate and kidney tumour.

At the ultrastructural level, using extravidin–gold to detect the bound biotinylated endostatin, the binding to vessels of malignant bladder was as seen on light microscopy, in the perivascular matrix, including the endothelial basement membrane (Fig. 3A) and directly on the endothelial cell membrane and in the endothelial cytoplasm (Fig. 3B). Abuliminal and luminal membrane invaginations, also called caveolae, are the preferred binding site of endostatin (Fig. 3C). In bladder carcinoma, immunogold labelling to detect endogenous endostatin and its precursor collagen XVIII distribution showed a similar distribution of endostatin protein as for endostatin-binding sites. Endostatin was associated with fibre-like structures (Fig. 3F).
and in the endothelial basement membrane (Fig. 3D), in the cytoplasm and mainly on the abluminal and luminal surface of endothelial cells of tumour vessels (Fig. 3D–F). Immunogold staining was also detected in the cytoplasm of the endothelial cells (Fig. 3D–F).

**DISCUSSION**

Endostatin is a potent inhibitor of angiogenesis and tumour cell growth, while having no effect on a resting vascular system [1,7]. To understand which vessels might be influenced by endostatin, we analysed the binding behaviour of endostatin to normal and malignant tissues are dissimilar at the molecular level, and endothelium derived from tumours is qualitatively different from that obtained from normal tissue [14]. These differences between endothelial cells in normal and malignant tissues could explain the diverse endostatin binding patterns in the vessels of the present tissues. Eberhard et al. [15] showed that vessels in tumour tissues can be selectively targeted without affecting the quiescent organ vascularity. This is explained by the different molecular phenotypes of immature angiogenic blood vessels, which are distinct from resting blood vessels [14]. Subsequently, many animal studies have shown the feasibility of selectively targeting actively proliferating vascularity, without affecting normal organ vascularity [7,16–18]. Therefore the tumour vascular bed is a possible therapeutic target for cancer treatment [19].

A different form of functional immaturity could also explain the variations in endostatin binding behaviour between bladder tumour vessels and those in kidney tumours. There may be discrepancies in the angiogenic potency of various kinds of endothelial cells, as has been described by others, who found both anatomical and angiogenically active vessels [20,21].

The distribution of bound endostatin, and thus the distribution of its binding sites, is in accord with published binding sites for endostatin, and indicates different binding sites on endothelial cells in the surrounding matrix. For cell-surface binding, glypican could be the corresponding site. Glypican, a cell-surface proteoglycan, which can also be released in the extracellular matrix [22], was described as a lower affinity receptor for endostatin [23]. A further candidate for endostatin binding to the cell surface is KDR/Flk-1. Kim et al. [24] described an endostatin-mediated blocking of vascular endothelial growth factor (VEGF) signalling by binding to the VEGF-receptor KDR/Flk-1. For intracellular binding, tropomyosin could be the binding site; McDonald et al. [24] described the binding of endostatin to tropomyosin and to tropomyosin-associated microfilaments in a variety of endothelial cell types. The intracellular binding of endostatin to tropomyosin, which is important in the contraction and morphogenesis of cells by influencing the regulation of the actin cytoskeleton [25], might explain the...
morphological changes associated with endostatin [5,7,12]. By comparing the distribution of endostatin-binding sites, detected by immunogold labelling on bladder tumour, with the distribution of endogenous endostatin/collagen XVIII provides an indication that there is a dependency between endogenous endostatin and its binding sites.

Thus, endostatin is bound in most vascular endothelial cells in malignant bladder and prostate tissues, but significantly less so in endothelial cells from malignant kidney tumours. Further studies should show whether endostatin binding correlates with haematogenous metastasis and causes a stable phenotype in superficial bladder tumour vessels, which leads to a low incidence of haematogenous metastasis in these malignancies [26]. The same reasoning could also be used to explain the similarly low incidence of haematogenous metastasis in the vessels of cancerous prostate tissue [27–29]. Furthermore, the weak or absent binding of endostatin to vascular endothelial cells in malignant kidney tissues could explain the relatively high incidence of haematogenous metastasis in these tumours [26]. As noted, possible variations in endothelial phenotypes might explain this characteristic and may subsequently lead to a more aggressive growth pattern for malignant kidney tumours than in superficial bladder tumours.

Further investigations should determine whether malignant bladder, prostate and kidney tumours could be further classified into those responding to endostatin or not, and whether this has prognostic value.

ACKNOWLEDGEMENTS
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CONFLICT OF INTEREST
None declared.

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Correspondence: Wilhelm Bloch, Department of Molecular and Cellular Sport Medicine, German Sport University Cologne, Carl-Diem-Weg 6, 50933 Cologne, Germany.
e-mail: W.Bloch@dshs-koeln.de

Abbreviations: TBS, Tris-buffered saline; PECAM, platelet endothelial cell adhesion molecule; VEGF, vascular endothelial growth factor.
The hunt for pink Viagra

Have we ever considered who is looking for what, in whom and why? The immediate assumption is that the pharmaceutical industry is driving the whole 'pink Viagra' process, as much to benefit shareholders as patients. It would appear that the impetus has come from several 'penis-envy, pressure groups' campaigning along the lines of 'what men have we must have', but would industry react to this type of pressure or has the hunt for pink Viagra been 'created' by the pharmaceutical industry?

Assuming that the pharmaceutical industry is driven by profit, does the maths indicate that a drug for the treatment of 'female sexual dysfunction (FSD)' would be commercially viable? In today's terms it costs £400–700 million to take a product to market (the actual cost of any one successful drug is actually much less, but the cost of the ≈92% of drugs that do not make it from bench to bedside have to be 're-absorbed' against marketed products). It costs considerably less to develop a drug for a second indication, e.g. doxazosin, which was originally developed for hypertension and subsequently for BPH, and duloxetine, an anti-depressant also being developed for stress incontinence. Potentially the commercial opportunity for FSD could be modelled on that of erectile dysfunction (ED). In 2004 the worldwide legal prescription market for ED is going to be close to $2.7 billion with sildenafil retaining a 60–65% market share, tadalafil retaining 20–30% and vardenafil retaining the rest. Although it has been calculated that the prescription market represents as little as 40% of total sales, it is the only component that the pharmaceutical industry has access to and can generate revenue from. When we factor in the development costs (above), profitability on each tablet (generally 70–85% for new drugs), annual marketing costs and patent life, the economics of the ED market can be interpreted in another way; sildenafil would be considered a 'blockbuster' by industry and stock market analysts alike, tadalafil might just about fit that description, and vardenafil would not even come close, with a <10% share of the ED market (in other areas, e.g. hypertension, such a market share would give rise to a 'blockbuster'). Any other phosphodiesterase inhibitors are likely to fare less well, and given the overall satisfaction with this drug class it is by no means certain that the entry of a new drug class in the future will either expand the market or even take market share.

The situation in FSD is even more complex; if nothing else because of the incomplete clinical definition and corresponding lack of consensus on clinical trial design. The scientists may well tell us that the prevalence of FSD is equivalent to that of ED, the degree of bother comparable, and potentially an analogous situation to that in ED could apply, with two or possibly three drugs becoming commercially successful. However, when we superimpose the heterogeneity encompassed within FSD, the economics become totally different for a drug reaching the marketplace. An effective drug, that is first to market and gains over 70% of the share for the arousal component of the FSD market (for the sake of argument let's say this represents 25% of the total FSD market), would become much less attractive. Peak sales incidentally would be ≈£500 million, with the third drug to the market gaining less than £50 million worldwide sales annually.

Based on this type of calculation, which is mandatory in the pharmaceutical industry
when considering a new therapeutic area, by and large the FSD opportunity would be considered unattractive, at least for initiating de novo research programmes. An additional negative factor is that, as relatively little is known about the pathophysiology of FSD, it would be almost impossible to select a mechanism on which to work. However, as described above, if FSD represented another indication for a product already marketed or soon to be marketed, the economics become considerably more attractive!

Not surprisingly, the pharmaceutical industry, or more correctly clinical investigators, started with the obvious, i.e. the use of sildenafil. Trials by Berman et al. showed a 17% increase in clitoral blood flow, and this translated into great expectations (and AUA abstracts) for the drug in FSD. Only with the completion of carefully controlled clinical trials by Pfizer has the true clinical potential of the drug been unravelled. Essentially the drug does not work in the general FSD population but could offer certain individuals some degree of benefit. Should we be surprised? I think not. At the clinical laboratory level, clitoral smooth muscle bears some resemblance, at least embryologically and biochemically, to corporal smooth muscle, and in both organs some degree of change in local blood flow and engorgement would be expected. As we do not know the inter-relationship between these physiological changes and FSD, the negative clinical trials data should not be surprising.

An approach with a more credible scientific pedigree has been the evaluation of various formulations of apomorphine in the arousal- and desire-deficient FSD clinical subpopulations. At least in terms of clinical anecdote, based on investigator-stimulated studies, some degree of benefit may be apparent with apomorphine sublingual (SL). However, the issue will be the risk in the benefit-risk equation, with the Food and Drug Administration holding particularly strident and negative views about the potential for syncope and fainting. Although the original developers for ED (Takeda, TAP and Abbott) are no longer pursuing the FSD indication for apomorphine SL, several other companies are, and with novel formulations, e.g. Nastech have a nasal delivery and Vectura a pulmonary delivery form of the drug. The wisdom of speeding up the absorption rate of a vasoactive agent with respect to orthostasis will, I am sure, be a subject of much debate with the regulatory authorities.

Not surprisingly, several companies with marketed hormone-replacement products (both oestrogenic and androgenic) have got in on the act and are undertaking some highly original clinical trials. These endocrine-based agents undoubtedly have as much scientific justification as any other approach (because of space and potential litigation issues these are not listed). However, Proctor and Gamble are to be applauded on completing two phase III studies on the use of their testosterone-replacement patch (Intrinsa) in women with hypoactive sexual desire disorder (HSDD). Presumably the use of androgens circumvents the negative perception of oestrogen-based hormone replacement therapy strategies. It remains to be seen whether the use of this testosterone delivery system, in the eyes of the regulators, avoids aromatisation to oestrogens.

I leave the reader to decide whether or not they feel that the pharmaceutical industry will: a) continue to try to develop products for FSD; b) base any such development on rational research programmes.

Next month I will review the pharmaceutical industry in China (PRC).

MICHAEL G. WYLLIE
Urodoc Ltd, Maryland, Ridgeway Road, Herne, Kent, CT6 7LN, UK
e-mail: mike@urodoc.co.uk
Utility of the fourth arm to facilitate robot-assisted laparoscopic radical prostatectomy

CHANDRU P. SUNDARAM, MICHAEL O. KOCH, THOMAS GARDNER and JONATHAN E. BERNIE

Department of Urology, Indiana University School of Medicine, Indianapolis, IN

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INDICATIONS

The robot-assisted laparoscopic radical prostatectomy (RALRP) is being increasingly used in several centres around the country. Robotic assistance enables the transfer of open surgical skills to an advanced laparoscopic operation with minimal previous laparoscopic experience [1]. Robotic assistance, even for skilled laparoscopic surgeons, could facilitate more accurate dissection because of the instruments with six degrees of freedom. It could also facilitate a watertight anastomosis because of the ease of laparoscopic robot-assisted intracorporeal suturing. However, robot-assisted surgery requires skilled laparoscopic surgical assistance by the patient’s side for active assistance without close supervision of the lead surgeon, who is at the console. Instruments held by the assistant may also be moved inadvertently by the instruments held by the robotic arms. The fourth arm for the da Vinci™ surgical system (Intuitive Surgical, Sunnyvale, CA) has been recently introduced. The arm is controlled by the operating surgeon and all the available da Vinci instruments can be attached to this arm. During the last 15 RALRPs we have successfully used the fourth arm throughout the operation.

METHOD

The RALRP is performed via a transperitoneal approach initially described by Guillonneau et al. [2]; over the last 5 years of performing LRP we have made several minor changes, as previously described [3,4]. Over the last year we have begun using robotic assistance and now use it for all LRPs. The technique of RALRP was previously described [5,6] in detail. The assistant is usually a laparoscopic fellow or a senior resident. In six patients, two attending urologists jointly performed the operation. The surgery is described with special emphasis on the variations from the Montsouris technique and the use of the fourth arm.

The patient is firmly secured to the operating table with his legs comfortably supported in a low modified lithotomy position, using Allen stirrups. Shoulder braces are not used, as these have on one occasion resulted in shoulder injury. The chest is secured to the table with adhesive tape, ensuring that this does not interfere with respiratory movement. The patient is placed in a Trendelenberg position before draping, to confirm that there is no movement of the patient on the table. The patient is then placed supine to obtain pneumoperitoneum. A Foley catheter is inserted urethrally to drain the bladder. Pneumoperitoneum is established at the umbilicus and the trocars positioned as depicted in Fig. 1. The trocar for the fourth arm is placed ≈3 cm above and medial to the anterior superior iliac spine on the left side. This is to ensure that there is adequate space between the working left arm and the fourth arm.
arm of the da Vinci surgical system. Significant interference between the arms can occur should they be close to each other. The assistant stands on the right side of the patient and the fourth arm is positioned on the left of the patient (Fig. 2). It is possible for these positions to be reversed. Unlike with the other working arms, the fourth arm may be ‘clutched’ to bring it to an appropriate position before it is docked to the daVinci trocar. The da Vinci 30° laparoscope, facing up, is first used to make a peritoneal incision from one medial umbilical ligament to the other. Both medial umbilical ligaments are divided to ensure adequate access to the pelvis. The umbilical ligaments and the urachus are dissected away from the anterior abdominal wall to enter the retropubic space. The bladder is not distended, as the plane is easily identifiable and no bladder injury has occurred.

The patient is placed in a steep Trendelenberg position before the robot is docked to the patient. The degree of the Trendelenberg position depends on the pelvic anatomy and the position of the bowel within the pelvis. The fourth arm can be used to retract the bowel and keep it away from the pelvis (Fig. 3). This can be done either by holding one of the appendices epiploicae attached to the sigmoid colon, or by retracting the colon with the shaft and elbow of the daVinci Prograsp™ instrument, with the jaws flexed. Prograsp is a grasper with a blunt tip that securely holds tissue but is not traumatic. The use of the fourth arm to help keep the small and the large bowel out of the pelvis enables the patient to be in less of a Trendelenberg position than that which would be required without the help of the fourth arm to retract bowel from the pelvis. This can be important in obese patients and while learning RALRP, when the operation could be prolonged. Furthermore, the inclination of the table cannot be reduced after the robot is docked, unless the instruments are removed and the robot is undocked.

The endopelvic fascia is divided and the lateral prostatic dissection performed. The puboprostatic ligaments are partially divided before suturing the deep dorsal venous complex with 20 cm 1/0 polyglactin suture on a CT-1 needle (Ethicon Inc, Sommerville, NJ). The remaining portion of the same suture is then used to insert a stay suture in the mid-anterior aspect of the prostate. This stay suture is then held by the Prograsp instrument on the fourth arm, and held anteriorly by the fourth arm, thereby enabling the bladder neck to become visible.

The bladder neck is then dissected by separating it anteriorly from the base of the prostate. Once the anterior bladder neck dissection is completed the Foley catheter that was previously inserted is brought out through the opening of the bladder neck anteriorly. The fourth arm is then used to hold the tip of the Foley catheter (Fig. 4). To facilitate anterior retraction of the prostate effectively, the Foley catheter is anchored to the drapes at the other end. With the Foley catheter held anteriorly, the posterior bladder neck dissection is facilitated. The posterior bladder neck is divided and the vas deferens identified in the midline. Once the vasa deferentia on both sides are dissected and divided, the seminal vesicles are dissected. At this stage of the operation, the vas deferens can be held by the fourth arm, but active retraction of the vas deferens by the assistant

FIG. 1. The trocar positions for RALRP. Large dots show the 12 mm, medium dots the 8 mm and the small dot the 5 mm daVinci trocars.

FIG. 2. The fourth arm of the robot approaches the patient below the left thigh, to be attached to the left lateral trocar.

FIG. 3. The fourth arm assists with retraction of the sigmoid colon and bladder before dissecting the endopelvic fascia.
is preferable, to help dissect the seminal vesicles.

Once both the seminal vesicles have been dissected in their entirety, Denonvilliers’ fascia is transversely incised to visualize the perirectal fat. The prostatic vascular pedicles are placed on stretch by holding both the seminal vesicles as well as the vas deferens anteriorly. This can be done by the fourth arm or by the assistant. The pedicles are then dissected, ensuring that the neurovascular bundles are preserved. At this point, the lateral pelvic fascia can be divided and the dissection carried out to separate the neurovascular bundles from the posterolateral aspect of the prostate. Alternatively, this can be done after the pedicles are divided. The perirectal fat is identified and the dissection continues posterior to the prostate until the apical region of the prostate is encountered. With the prostate completely freed laterally as well as posteriorly, the apical prostate is dissected, using bipolar forceps and scissors. The dorsal venous complex is divided and the urethra identified. The urethra is sharply divided with scissors. The monopolar hook is not used to divide the urethra as it is possible that any tissue injury with coagulation could impair tissue injury. In the passing of instruments through the assistant trocars is done outside the range of laparoscopic visibility. Inadvertent injury to the bowel can therefore occur should the assistant not be aware of the potential for this significant complication. The aggressive suction during the operation and depletion of the gas for pneumoperitoneum can result in complete desufflation of the abdomen. This can result in the da Vinci trocars being dislodged from the abdominal cavity. The operating room table should not be moved after the da Vinci has been docked, as this can result in significant injury to the patient because the da Vinci surgical system is independent of the operating table, and the trocars are fixed to the da Vinci arms.

ADVANTAGES AND DISADVANTAGES

The fourth arm, as described, is a useful tool during RALRP; its use facilitates greater control by the operating surgeon, enabling the surgery to be conducted with less experienced assistance. The fourth arm is especially valuable in residency programmes, where residents would need to be exposed to robotic-assisted surgery, and could have varying degrees of laparoscopic skills and experience. However, despite the use of the fourth arm, it is important that the bedside surgical assistant is aware of the basic principles of laparoscopy. The assistant continues to play an active role in the operation, for suction, active retraction, and the passing and retrieval of suture and needles from the abdomen. The vast majority of the passing of instruments through the assistant trocars is done outside the range of laparoscopic visibility. Inadvertent injury to the bowel can therefore occur should the assistant not be aware of the potential for this significant complication. The aggressive suction during the operation and depletion of the gas for pneumoperitoneum can result in complete desufflation of the abdomen. This can result in the da Vinci trocars being dislodged from the abdominal cavity. The operating room table should not be moved after the da Vinci has been docked, as this can result in significant injury to the patient because the da Vinci surgical system is independent of the operating table, and the trocars are fixed to the da Vinci arms.

In conclusion, robotic assistance has significantly facilitated the laparoscopic approach to RP. The recently introduced fourth arm can be used effectively for LRP without increasing the invasiveness of the procedure.

CONFLICT OF INTEREST

None declared.

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**Correspondence:** Chandru P. Sundaram, Indiana University School of Medicine, 535 N Barnhill Drive, Suite 420, Indianapolis, IN 46202, USA; e-mail: sundaram@iupui.edu

**Abbreviations:** RALRP, robot-assisted laparoscopic radical prostatectomy.
Unrecognized bladder perforation while placing a suburethral synthetic sling: a minimally invasive technique for removing an intravesical sling segment

LEWIS W. CHAN and VINCENT W. TSE
Department of Urology, Concord Repatriation General Hospital, Sydney, Australia
Accepted for publication 5 August 2004

METHOD
A 71-year-old woman presented with recurrent UTIs, suprapubic and perineal discomfort 9 months after placement of an IVS for stress urinary incontinence. Cystoscopy showed that a segment of the sling had perforated the bladder on the left wall, just proximal to the bladder neck, extending from the 1 o’clock to the 5 o’clock position. Under cystoscopic guidance a 5-mm laparoscopic port was inserted suprapubically into the bladder. The intravesical segment of the IVS was then grasped with flexible alligator grasping forceps transurethrally and placed under tension (Fig. 1). The laparoscopic scissors were then inserted from the suprapubic port and the intravesical segment of the IVS was then divided flush on the bladder mucosa with the bladder fully distended (Fig. 2). The sling segment was then removed urethrally. Inspecting the site of bladder perforation from the suprapubic port confirmed no residual sling material within the bladder (Fig. 3). A urethral catheter was placed for 1 week. The patient’s symptoms resolved after removal of the sling segment and cystoscopy at 3 months showed good healing of the bladder with no visible sling material.

COMPARISON WITH OTHER METHODS
The incidence of inadvertent perforation of the bladder while placing a suburethral sling such as the TVT has been reported to be <5% [2]. If immediately recognized at cystoscopy the problem is easily rectified by replacing the trocar. However, the common sites of perforation are just proximal to the bladder neck and it is important to use the 70° cystoscope lens to inspect this region. If the injury is not recognized immediately the patient may subsequently have symptoms of irritative voiding, pain, infection or calculus formation. The intravesical segment of tape can be removed by open cystotomy [2], which has the potential morbidity of wound complications and difficult retropubic dissection in patients who have previously undergone colposuspension procedures. Cystoscopic division of the tape transurethrally is difficult because of the need...
to place the tape segment under tension to enable division as close to the bladder mucosa as possible, to minimize residual tape material being left in the bladder. The present method avoids the need for an open cystotomy while allowing precise division of the tape flush with the bladder mucosa, viewed at right angles from the examining cystoscope. As with experience reported elsewhere, the present patient had no recurrence of stress urinary incontinence after removal of the sling fragment.

CONFLICT OF INTEREST

None declared.

REFERENCES


Correspondence: Lewis W. Chan, Department of Urology, Concord Repatriation General Hospital, Hospital Road, Concord, NSW 2139, Australia.
e-mail: chanle@email.cs.nsw.gov.au

Abbreviations: IVS, intravaginal slingplasty; TVT, tension-free vaginal tape.
A TECHNIQUE FOR PLACING INFANTS IN THE LITHOTOMY POSITION USING TOWEL ROLLS

Sir,

I read with interest the article by Tan et al. [1]; putting patients in the lithotomy position has always been a subject of concern [2–4]. The idea of using silicon headrests for this position is interesting, but when the ankle is fixed as described by authors, it (together with the hip joint) will act as a fulcrum, on which the knees will swing from side to side. This instability will be clumsy during operative procedures.

Putting an infant in the lithotomy position is not difficult if the basic anatomical differences between the hip joint of infants and adults is appreciated. In infants the acetabulum is shallower than that of adults. The head of the femur is also larger and nearly a third of it lies outside the acetabulum [5]. Moreover, the ligamentum teres is longer in infants. All these factors together allow a greater range of mobility of the infant hip joint. The flexed hip of infants can be abducted to 90° so that both the knees can simultaneously touch the couch, a movement impossible in adults. Urologists wishing to place an infant in the lithotomy position should use this anatomical advantage. Using this principle, I suggest the following technique, which I have used for the past 8 years.

The perineum of the infant is brought to the edge of the operation table. Both hip joints are symmetrically flexed, abducted and externally rotated. A towel roll of appropriate size is placed, one on either side, below the flexed knees (Fig. 1a,b). The towel rolls are kept lateral to the hip joints but medial to the ankle joints, supporting the knees. The infant is secured in this position using adhesive tapes. This gives unhindered access to the perineum and abdomen.

I have used this technique in several hundred children since 1997, for cystoscopy, urethroplasty, bladder surgery and anorectal operations. This technique is applicable to children aged <3 years. I have operated for up to 8 h with the patient in this posture, with no adverse consequences. As the towel rolls are soft, pressure effects and neuropraxia are unlikely. Radiolucent cloth rolls permit on-table radiography. As the size of towel rolls can be customized, and as they are universally available, they are a better option than silicon headrests for placing infants in the lithotomy position.

VENKATACHALAM RAVEENTHRAN,
Division of Pediatric Surgery, Rajah Muthiah Medical College, Annamalai University, Tamilnadu, India

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RADIONUCLEIDE BONE SCINTIGRAPHY IN PATIENTS WITH BIOCHEMICAL RECURRENCE AFTER RADICAL PROSTATECTOMY: WHEN IS IT INDICATED?

Sir,

We read with interest the suggestion made by Gomez et al. [1], that taking bone scans in patients with a serum PSA level of <7 ng/mL during biochemical recurrence after radical prostatectomy (RP) is unlikely to be positive, and that clinicians should request bone scans for patients with a PSA level of >7 ng/mL. Serum PSA is a useful predictor of disease recurrence after surgery but it is difficult to distinguish between local recurrence and distant metastases. Studies assessing the usefulness of bone scans in this situation have produced conflicting advice as to when scanning is appropriate and if a PSA threshold can be used. In 1991, Terris et al. [2] recommended that patients with detectable PSA levels after RP should routinely have bone scans, while Partin et al. [3], after evaluating 51 men with PSA-only recurrence after RP, recommended annual bone scans in patients with biochemical recurrence. However, 60% and 70% of patients with positive bone scans in both these studies had nodal metastases at RP. Lee and Oesterling [4]

FIG. 1. A, The lithotomy position using towel rolls, and B, the same child in lateral view.
concluded from their experiences that it would be reasonable to omit bone scans in patients with recurrent prostate cancer after RP when their PSA was <2 ng/mL. Cher et al. [5] showed that the probability of a positive bone scan was <5% until the PSA increased to 40–45 ng/mL, while Jhaveri and Klein [6] concluded that bone scans in patients with a PSA recurrence after RP have limited usefulness until the PSA is >30 ng/mL. The sensitivity of serum PSA for predicting bone metastases may also be affected by adjuvant hormonal therapy after RP. In a study by Koizumi et al. [7] two of the six patients on hormones had developed bone metastases although their PSA levels were low.

Gomez et al. suggest a PSA threshold of 7 ng/mL, but their study is flawed; they included patients being staged before possible salvage therapy, and those with symptoms suggestive of metastatic disease, but these two groups might more usefully be considered separately. The inclusion of one symptomatic patient with a high PSA value (100 ng/mL) and positive bone scan is likely to have skewed the mean value of PSA in patients with a positive scan. In addition, the study group was highly selected; although 153 patients had a biochemical recurrence, only 35 of them had a bone scan. The reasons for not scanning the other 118 were not explained. Finally, three of the group of 35 patients were excluded, but their results seem to have been included in the analysis, which again may have influenced the final PSA threshold.

At present, bone scintigraphy is still the standard for detecting bone metastases, but is likely to be negative in patients with a low PSA level after surgery. However, in our view the published data do not clearly define a PSA threshold below which bone imaging should not be used; this could only be achieved by a large prospective study. In addition, evidence is accumulating that adjuvant radiotherapy after RP is only effective at low PSA levels, but in this situation spread to bone is usually by micrometastases which are not reliably identified by any of the current imaging techniques. In the future, bone-specific biochemical markers may be a better way of detecting prostate cancer recurrence in these patients.

RAMESH THURAIRAJA, JONATHAN P. McFARLANE* and RAJENDRA PERSAD, Departments of Urology, Bristol Royal Infirmary and "Royal United Hospital Bath, UK

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PROSTATE SIZE INFLUENCES THE OUTCOME AFTER PRESENTING WITH ACUTE URINARY RETENTION

Sir,

I am concerned that the article by McNeil et al. [1] made no reference to an identical study from our unit which was published in the BJU Int only 4 years ago, and which reached exactly the same conclusion [2]. Perhaps this was an oversight. The lapse is unfortunate, particularly as Mr McNeil criticised our study for using the DRE as a means of assessing prostate size. His precise comment at that time read: ‘I do not think conclusions can be drawn about how prostate size may influence the outcome after AUR until a study is conducted using a reliable method for accurately assessing prostate size’ [3]. I note that prostate size in his present study was based on a DRE ‘by the admitting urologist’. There is no mention of grade of trainee or how many individuals conducted the examinations, in contrast to our (uncited) study in which the DRE was by the experienced finger of one consultant urological surgeon. Has Mr McNeil had a change of heart as well as a memory lapse?

PAUL P. IRWIN, Consultant Urological Surgeon, Michael Heal Department of Urology, Leighton Hospital, Crewe, UK

1 McNeil AS, Rizvi S, Byrne DJ. Prostate size influences the outcome after presenting with acute urinary retention. BJU Int 2004; 94: 559–62

PRENATALLY DIAGNOSED UNILATERAL RENAL PELVIC DILATATION: A DYNAMIC CONDITION OF ULTRASOUND AND DIURETIC RENOGRAPHY

Sir,

These authors [1] highlighted that their study was not randomized and therefore have been guarded in their conclusions, and recognize the retrospective nature of their work. However, the conclusion that the data support the benign nature of prenatal unilateral hydronephrosis needs to be challenged; the conclusion is true for a portion of cases, but not all.

There is no doubt that in most cases of prenatal pelvic dilatation it will resolve, but not all pelvic-ureteric obstruction has the same cause and not all kidneys have a benign course. Some patients have infection, stone formation and loss of function, and
Presenting with pain, and had lead to the child reported who had the obstruction, it was experiencing pain and had significant improvement in some, particularly as we do not know the infection history. (x) A history of obstruction and better functioning that those surgically treated. (iii) As the study was retrospective, some patients treated by surgery may have been over-treated. (iv) There is no recording of the operative findings that would allow for validation of the decision to proceed to surgery. (v) The follow-up in the study is very short, too short to realistically assess the impact of the decision on prognosis. (vi) There is no mention of the clinical history of pain, infection, stone formation; if these were present then surgery would be more appropriate. (vii) A tense kidney on palpation would appropriately undergo surgery, and should not be considered benign. (viii) Changes on ultrasonography consistent with high intrarenal pressure should be considered additional information to promote surgical treatment, including hyperperistalsis of the pelvis, marked calyceal dilation with thin parenchyma, and the eggshell sign [2,3]. (ix) Prenatally diagnosed unilateral renal pelvic dilation: a dynamic condition on ultrasound and diuretic renography. J Urol 2004; 172: 1456–9

For the best treatment of all cases, and to avoid situations like the meningitis case, a more individualized approach to patients with significant dilation would seem appropriate, rather than the general conclusion that unilateral hydronephrosis is benign being applied to all patients.

**LIFELONG PREMATURE EJACULATION: FROM AUTHORITY-BASED TO EVIDENCE-BASED MEDICINE**

Sir,

In response to my article on evidence-based research of lifelong premature ejaculation [1], Denniston and Hill expressed their concern that circumcision was not mentioned as an important factor in the development of premature ejaculation [2]. With their reference to the studies of O’Hara and O’Hara [3] and Gemmell and Boyle [4], readers may erroneously have the impression that circumcision is considered as a scientifically accepted risk factor for developing premature ejaculation. My current reply mainly considers the notion that both references are methodologically insufficient. For example, O’Hara and O’Hara [3] reported about women who had experienced intercourse with both circumcised and intact partners. These women stated that more of their circumcised than intact partners had premature ejaculation. However, notably in this study, premature ejaculation was defined as having an orgasm within 2–3 min in more than half the attempts. Apart from this arbitrary definition of premature ejaculation, the analysis was based on an open-label retrospective design with a questionnaire, assessing subjective judgements of these women. In other words, the actual ejaculation time of the men reported was not prospectively recorded with an objective timer.

Indeed, the presence or absence of a prepuce may be influential on how intercourse or other forms of sexual contact is conducted and experienced by both partners. However, no information about the exact role of circumcision on the development of ejaculatory disorders has been provided by evidence-based studies. A scientific and realistic way to obtain basic information on this issue is to conduct population-based studies among different cultures, using stopwatch analysis of the intravaginal ejaculation latency time (IELT) [5]. Only comparison of the IELT distribution in both circumcised and intact men (with no genital diseases) and within and between cultures or countries will provide answers on the role of circumcision as a risk factor for developing either lifelong premature or delayed ejaculation.

**MARCEL D. WALDINGER,**

Department of Psychiatry and Neurosexology,
Leyenburg Hospital, The Hague, The Netherlands

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A COMPARISON OF LYCOPENE AND ORCHIDECTOMY VS ORCHIDECTOMY ALONE IN THE MANAGEMENT OF ADVANCED PROSTATE CANCER

Sir,

A previous issue of BJU Int [1] included a report of a remarkable response by metastatic prostate cancer to low-dose lycopene in addition to orchidectomy. Unfortunately, the Kaplan-Meier curve in the article obviously did not correspond with the reported results, as it showed shorter survival for the orchidectomy + lycopene group (O+L) than the orchidectomy-alone (O) group, and many more deaths in total than had occurred in the study. In response to my letter to the Editor [2], a new legend, identifying the former O+L curve as the O curve and vice versa, was published as an erratum in the same issue. A reply by the authors appeared in September 2004 [3], in which they say that they have reviewed their data, reaching the same results, but do not comment on the question about the number of deaths in the study.

The remaining comment is, therefore; in the Results it is stated that 12 of 27 patients in the O group and seven of 27 in the O+L group died during 24–28 months of follow-up, i.e. survivals of 56% and 74% at the end of the study. The Kaplan-Meier curves show survival at 27 months of ≈20% in both groups. As the reported results will affect prostate cancer treatment profoundly if repeated by other researchers, I would very much appreciate a reply from the authors on this specific inconsistency.

OLA BRATT, UROLOGIST, Lund University Hospital, Sweden

THE DIFFICULT URETHRAL CATHETERIZATION: USE OF A HYDROPHILIC GUIDEWIRE

Sir,

With regard to this report [1], the concept of using hydrophilic guidewires and/or ureteric dilators is not new. Blitz [2] proposed a technique where a urethral catheter was loaded over a hydrophilic guidewire with the aid of an intravenous catheter. Dewan et al. [3] presented their experience with dilatation of urethral strictures using a guidewire and sheath dilator technique in paediatric patients. Zammit and German [1] presented their interesting experience with the use of a hydrophilic guidewire, a 16 F urethral catheter and/or 6–12 F semirigid ureteric dilators. In a recent study (unpublished data) we successfully used a combination of both a straight flexi-tip 0.09 mm hydrophilic guidewire (Terumo Radiofocus Guide Wire M) and a 14/16 F ureteric access sheath (Forte, Applied Medical). Hydrophilic coatings have proved their efficacy and atraumatic characteristics within the ureteric lumen. Based on the existing experience in the ureteric lumen we decided to use the same concept within the larger diameter urethral lumen. The development of larger diameter hydrophilic sheaths may lead to a totally atraumatic 'one step' management of urethral strictures.

ANASTASIOS ATHANASSOPOULOS, EVANGELOS N. LIATSIKOS and GEORGE A. BARBALIAS, Department of Urology, University of Patras, Rion, Greece

1 Zammit PA, German K. The difficult urethral catheterization: use of a hydrophilic guide wire. BJU Int 2004; 93: 883–4
INTRODUCTION

Worldwide, the commonest cause of vesicovaginal fistulation (VVF) is obstructed childbirth, but, in obstetrically developed countries this is usually a complication of pelvic surgery, most commonly hysterectomy. It is almost always technically possible to close a VVF, even when the local tissue healing is compromised by irradiation changes but, in any particular case, a satisfactory functional result naturally depends on the competence of the residual sphincter mechanisms. To achieve primary closure of any fistula reliably, the surgeon must be equally experienced in both the vaginal and the various abdominal approaches: the distinction between a ‘simple’ and a ‘complex’ fistula is critical to selecting the one that is most appropriate.

The healing quality of the tissue margins of a ‘simple’ fistula are virtually normal so these can be reliably resolved by a simple, meticulously sutured, layer-closure; however, where appropriate local tissue is readily available, the additional interposition of a pedicled flap of this between the suture lines can virtually guarantee the expected success of the procedure. Failure to close a simple fistula reclassifies it as ‘complex’: in appropriately experienced hands, this should be a very rare event.

The resolution of a ‘complex’ fistula is generally very much more difficult and the result less reliable; success almost always depends on the interposition of a well-vascularised tissue layer. A vaginal fistula may be regarded as ‘complex’ for various reasons, amongst them extensive tissue loss, developmental deficiencies, the impaired healing potential of its margins, and all fistulae that involve the sphincter mechanism, post-obstetric and urethro-vaginal.

This short summary can offer no more than an outline of the various principles, considerations and procedures involved in the repair of VVF; we have recorded further details of all of these elsewhere [1].

PLANNING AND PREPARATION

The most important single factor in avoiding any postoperative complication or surgical injury to the lower urinary tract is a real awareness of the possibility that it can easily happen and every reasonable precaution must be taken to avoid it. Prevention is therefore far better than cure, and it is essential that, in addition to meticulous surgical technique, the surgeon should have an accurate knowledge of the relevant surgical anatomy of the ureters and the anatomical relationships of the base of the bladder, in particular its relationship to the vascular pedicles of the uterus and vagina. Appropriate surgical access is critically important, to overcome the confines of the pelvic cavity that naturally restrict this. Careful positioning of the patient and planning of the approach are essential,
together with an efficient retractor system.

**INDICATIONS**

It is relatively uncommon for even smaller VVF to close in response to conservative treatment by simple catheter drainage of the bladder. Early and effective definitive closure is therefore strongly advocated. Traditionally, the repair of VVF used to be deferred for 2–3 months to ensure that the initial local tissue healing reaction had settled beforehand. In recent years a major advance in managing postoperative fistula has been immediate repair, unless specifically contraindicated, e.g. because of massive haematoma or infection. The development of a urinary fistula after a pelvic surgical procedure should be regarded as a diagnostic and urological emergency. Immediate specialist referral is important because a 'hopeful delay' is likely to result in missing the optimum 'window of opportunity' for an early repair, with all its consequences, medical, psychological and medicolegal. After 2–3 weeks the local tissue reaction may make a repair more difficult and precarious, so it may be then advisable to defer definitive repair for 2–3 months or more to ensure that this has settled.

**SPECIFIC EQUIPMENT/MATERIALS**

Appropriate instrumentation can greatly facilitate fistula repair. A ring retractor is recommended, along with a variety of fixed and malleable copper blades.

- An additional self-retaining retractor for vaginal surgery, e.g. Parkes anal retractor
- Curved needle holders (Turner Warwick)
- Additional targeted lighting, delivered either with the aid of a fibre-light 'sucker' or an appropriate headlamp.
- Cysto-urethroscope with a ureteric catheterization bridge (30° telescope).
- Ureteric catheters
- 16 F silicone Foley catheters
- Standard operating instruments at the preference of the surgeon.

**THE DIAGNOSIS OF A VVF**

Most VVF are easy to identify; those associated with thin-walled bladders, in the midline above the trigone, may be large enough to feel with the tip of a finger in the vagina. Conversely, a long-established 'pin hole' fistula at the base of the bladder is not associated with the use 'tell-tale' hyperaemia around its margins, and it may be difficult to identify endoscopically. If the appearance is equivocal it may be helpful to distend the bladder with irrigation fluid, with the patient in the lithotomy position, and to observe the anterior vaginal wall for a jet or a drip leakage, using a speculum in the vagina and a fibre-light sucker. Alternatively, examination of both the bladder and the vagina with a cystoscope, with gentle probing of suspicious areas with a guidewire, can also be extremely helpful, as catheterization of a fistula which might not be easy to detect can suddenly make the situation much clearer. It is important to remember that there may be more than one fistulous track, especially after the failure of a previous repair procedure.
The 'three-sponge' test can be helpful as an adjunct to bladder examination in identifying the source of a small urinary VVF that is difficult to locate. This simply involves placing three separate and suitably sized gauze sponges to gently fill the vagina, one above the other (Fig. 1a). Coloured fluid, e.g. aqueous methylene blue, is then introduced into the bladder with a catheter (Fig. 1b), and the three sponges removed after \( \approx 10 \) min. Remember to remove the urethral catheter after filling the bladder, to avoid masking a urethrovaginal fistula.

(1) If only the lower-most sponge is coloured, it suggests that the leakage has come down the urethra, indicating either a low urethral fistula or simply urethral incontinence back-tracking into the introitus (Fig. 1c).

(2) If both the lower sponges are unstained and the top sponge is wet with unstained urine it generally indicates a uretero-vaginal fistula (Fig. 1d).

(3) If only the upper sponge is stained it suggests a VVF (Fig. 1e). Very occasionally dye staining of the uppermost sponge can result from reflux of the dye from the bladder into the ureter and its leakage from a uretero-vaginal fistula (Fig. 1f).

The number of knots in the draw-string of each of the sponges indicates their level in the vagina after their removal.
The options for the open surgical repair of a VVF are:

A vaginal approach. The positioning for a vaginal approach can either be with the patient in the standard lithotomy position (Fig. 2a) or in the modified Sims position (Fig. 2b).

An abdominal approach. A synchronous perineo-abdominal approach (PAPA); when operating via an abdominal approach it is also sensible to have the patient in the perineo-abdominal position so that manipulation of the vagina is easy and progression to a PAPA facilitated. We do not use the standard 'legs together' supine position when operating in the pelvis.

Irrespective of whether the primarily intended approach for a fistula repair is vaginal or abdominal, the perineum and abdomen are prepared and draped in a single sterile operating field for a synchronous procedure. When appropriate, mild additional flexion of the hips can be used for a vaginal approach in the PAPA position, because this is easily flattened in the event of a need for a synchronous abdominal approach. However, care must be taken to avoid the complication of the anterior compartment syndrome that can result from calf-pressure supports, such as the Lloyd-Davies, during prolonged operations [1].

During a definitive abdominal approach the synchronous vaginal access provided by the single sterile perineo-abdominal operating field of the PAPA position has particular advantages for VVF repair.

1. It enables the placing of a finger in the vagina to guide the separation of the fused vesico-vaginal tissue layers around the fistula.

2. Bleeding that develops low in the abdomino-perineal interposition tunnel is often controllable by vaginal finger pressure until definitive haemostasis is secured.

3. It facilitates urethral catheterization and manipulation.

4. Synchronous peroperative endoscopy and instrumentation procedures are occasionally helpful.
Ureteric catheters facilitate the identification of the ureteric orifices and the extravesical location of the terminal ureteric segments while repairing bladder-base fistulae.

The vaginal orifice of the fistula is identified. Two stay-sutures are inserted into the vaginal wall anterolateral to it and directional traction on these, anchored in relation to the appropriate guide-knobs of the perineal ring retractor, effectively draw the fistula down to the introitus. The traction on these stay-sutures is generally preferable to the alternative procedure of traction on a balloon catheter passed through the fistula, because this has to be removed before layered closure of the bladder.

A third stay-suture is inserted into the vaginal wall in the mid-line above the fistula to stabilise its retraction. If laxity of the anterior vaginal wall does not allow this to be drawn down effectively to the introitus, it can be usefully retracted posteriorly using the guide-locating notch in the distal margin of the posterior vaginal blade of the ring retractors, with appropriate tension-anchorage at the ring margin.
The margin of the fistula is circumcised (dotted line); the excision of the peri-fistula scarring is facilitated by traction on additionally inserted stay-sutures. The layer between the vaginal wall and the bladder wall is developed.
Figure 6

The bladder wall is closed with an interrupted 4/0 polyglycolic acid (PGA) suture, the knots being tied on the lumen until the last two or three sutures are inserted. A Martius interposition flap is raised and tunnelled through to the fistula closure site.
Figure 7

The vaginal wall is closed; the Martius labial incision is occluded with 3/0 PGA dead-space-encircling sutures. Both a suprapubic catheter and a urethral catheter are positioned. When the prone position is used for a vaginal repair the suprapubic catheter is inserted with the patient supine before they are turned prone.
Figure 8

The ‘supra-pubic cross’ incision.

A midline incision can be performed in a cosmetic fashion via a Pfannenstiel skin incision followed by elevation of the skin and subcutaneous tissues up to the umbilicus.

This is important as many of these patients will have already had a Pfannenstiel incision at the time of a prior hysterectomy.

Very occasionally an additional short epigastric skin incision enables an upward extension of the midline incision to provide access for mobilisation of the omental pedicle.
Figure 9

The suprapubic cross incision is retracted with an abdominal ring retractor. The bladder and the vaginal vault are elevated up into the wound by suspension stay-sutures retained over the margin of the ring retractor. The elevated bladder is opened by a laterally curved vertical incision to facilitate its eventual closure. The bladder incision is extended down into the fistula itself (dotted line) and its lateral margins are retracted by elevating stay-sutures to expose the bladder base widely.
The ureteric orifices are identified; ureteric catheters are passed up to the kidney on either side and the distal ends exteriorised through the urethra into the sterile perineal-access approach of the PAPA position. These catheters can be passed endoscopically during the preliminary examination, but they are equally easy to pass during the operation. When the bladder is open and the ureteric orifices are obscured by inflammatory changes on the bladder base, they are more easily identified by observing the almost immediate efflux of clear urine generated by the intravenous injection of a diuretic, rather than by waiting for the relatively delayed excretion of an intravenously administered coloured dye such as indigo carmine.
Figure 11

The separation of the fused layers of the bladder and the vagina at the margin of the fistula is greatly facilitated by scissor-tip dissection guided by the tip of the surgeon’s finger in the vagina. Even when the adhesion is dense and extensive it is remarkably easy to define it by this sharp scissor-tip cutting at a level ≈ 3 mm from the fingertips, the thickness of the vaginal wall. This is simply estimated by finger tip sensation until the natural intervening tissue plane opens up.
The margins of the vaginal opening of the fistula are excised and it is closed by interrupted short runs of 3/0 PGA sutures.
Figure 13

Both a suprapubic catheter and a urethral catheter are inserted. The curved incision in the bladder is easily closed by simple rotation of its inherent flap using interrupted runs of 3/0 PGA sutures.
The space for omental interposition support of the suture line can be created either by simple lateral development of the space between the bladder base closure and the vaginal closure from above, or by the synchronous development of an abdomino-perineal tunnel, ≈5–8 cm wide that opens distally at the margin of the introitus behind the urethral meatus. In most cases it is not necessary to create a full abdomino-perineal tunnel of this sort.
Figure 15

The mobilised omentum is introduced into the interpositional space. An abdominal omental interposition is anchored at the upper margin of the interposition space, an abdomino-perineal tunnel interposition is fixed by including the distal margin of the apron with the sutures closing the introital incision at its lower end.
Figure 16

Complex vesico-vagino rectal fistula.

With the patient in the perineo-abdominal progression position the fistula is opened from above, separating the rectum from the back of the bladder. The stenotic vault of an irradiated vagina is excised. After its separation from the rectal wall posteriorly and the vesico-urethral wall anteriorly, the vaginal wall is circumcised transvaginally at the upper limit of its preservable viability and calibre.
Figure 17

Both a suprapubic and urethral catheter are positioned. The rectal and bladder walls are closed. The omental apron is mobilised to fill the sizeable gap between the bladder and the rectum, and its distal margin is included in the vaginal closure sutures. If a bowel-substitution vaginoplasty is indicated it can be done either as an immediate or a deferred procedure.
SURGICAL STEPS

BASIC PRINCIPLES

Absorbable suture materials should be used; interrupted sutures have been established to ensure the best possible vascularization of the tissue between the tissue 'bites' but the advantage accruing from this can be compromised by inflammatory reaction at the site of knots, and a rational comprise is the use of interrupted short runs. The routine use of effective prophylactic postoperative antibiotic cover is important. Adequate postoperative drainage of the bladder via both a urethral and a suprapubic catheter is recommended, as if one of these blocks the other would hopefully be patent, thereby protecting the bladder repair. This should be maintained after surgery until it has served its intended function; this depends upon the surgeon's judgement. As a general rule, if there is any doubt it is usually better to maintain catheter drainage a little longer rather than removing it too early, based on the principle of 'there should be no such thing as brave surgeons, just brave patients'.

TISSUE-INTERPOSITION SUPPORT

The principles of the layered closure of a fistula are well established. The adjuvant use of an additional supporting tissue is a generally advisable routine after a layered closure, whenever this is easily available. However, when the healing potential of the tissue around a fistula is compromised for any reason (e.g. diabetes, infection, infestation, the failure of previous repairs or irradiation) the reliability of a simple layered closure procedure diminishes and the failure rate rapidly increases unless a definitive well-vascularized transposition graft is interposed.

FLAPS OF LOCAL PERITONEUM

The transposition of a flap of pelvic peritoneum was described more than 100 years ago; this is sometimes useful as a simple adjuvant support of the layered closure of a 'simple' fistula, but its vascularization is not particularly good and it is quite inadequate when positive support is required as a result of significant local pathology that is likely to compromise healing (apart from it being itself commonly compromised by this local tissue abnormality).

PEDICLED FLAPS OF SKELETAL MUSCLE

Skeletal muscle has some inherent limitations as a supporting tissue: (i) Its 'resting' vascularization is minimal; this is only maximally augmented during muscular exercise. (ii) It is relatively poorly adapted to resist infection, thus it can disintegrate when repositioned into the severely infected surroundings of some complex fistulae. (iii) It is not especially adapted to resolve inflammation, so that it can contribute little to the local tissue healing when this is severely impaired. (iv) Inactivity of a muscle eventually results in disuse atrophy and it is largely replaced by fibrous tissue unless it is regularly exercised. However, a muscle flap that is adequately vascularized is most useful when the reconstructive requirement is a sizeable bulk of viable interposition tissue in a situation that is not grossly infected.

THE MARTIUS LABIAL ROTATION FLAP

A Martius flap provides useful vagino-urethral interposition support after a vaginal-approach layered closure of a fistula, and it was originally developed for this purpose. Its particular advantage is that it is locally available during a perineal approach with no synchronous abdominal approach. It requires careful mobilisation and redeployment [1].

It is a simple fat pad, which provides a thin, but reasonably well-vascularized tissue bulk. It has no special healing qualities, so it is by no means comparable to the omentum.

OMENTAL SUPPORT

The omentum is unique, as it is the only body tissue that is specifically developed for resolving inflammation. It has excellent vascularization and this must be preserved during its mobilisation; it is also capable of rapid augmentation in response to inflammation. It has an abundant lymphatic drainage which is so good that it can rapidly re-absorb macromolecular inflammatory exudates, the accumulation of which can otherwise create purulent collections that compromise the healing of a repair. Unlike the retroperitoneal and retropubic fat, the omentum regains its suppleness after an inflammatory response has settled, so it provides a unique mobile support that is fundamentally important to the reliable success of many functional reconstructions.

 Appropriately used, the omentum can almost guarantee the closure of the most complex VVF. It is the basis of 'salvage surgical procedures' after irradiation, and the success of these is often entirely dependent on the availability, and the meticulous transposition, of the vascular pedicle of the omental apron.

TRANSABDOMINAL FISTULA REPAIR

Technically, in terms of access and versatility, the supravesical abdominal approach provides superior access for the repair of many VVF; it is suitable for all such fistulae in all locations, down to and including the bladder neck and the proximal urethra. However, a vaginal-approach repair is a less extensive surgical procedure so this is naturally preferable when the circumstances are appropriate for it.

THE INCISION

A midline abdominal wall incision is essential to provide appropriate access for mobilising the full length of the vascular pedicle of the omentum from the stomach; this is necessary in about a third of cases in which omental interposition is required for the reliable repair of a complex VVF. The need for such an extensive mobilisation of the omentum cannot be predicted before surgery. A common clinical problem is that many of the patients who require repair of a VVF have just had hysterectomy using a Pfannenstiel incision approach, with a horizontal skin incision. An additional vertical midline skin incision for an omental fistula repair results in a scar that is a lasting reminder of the complication, and is best avoided.

THE ‘SUPRA-PUBIC CROSS’ INCISION

The 'supra-pubic cross' incision was specifically developed to enable the great majority of fistula repairs after a Pfannenstiel-approach hysterectomy to be completed through the original skin incision. After a slight lateral extension of this horizontal skin incision, the upper and lower skin and subcutaneous tissue flaps are separated from the rectus fascia, upwards and downwards, sufficiently to enable a midline abdominal wall incision to be made up to the level of the umbilicus and leaving the original horizontal Pfannenstiel rectus sheath closure intact. Suture reinforcement of the margins of
the previous horizontal sheath closure transsected by the midline incision is generally advisable.

In the event that an upper abdominal access is required to mobilise the vascular pedicle of a short omentum (30–40% of cases) this can be achieved by a short additional midline epigastric skin incision and a supra-umbilical extension of the midline incision in the abdominal wall, which is in continuity under the wide skin bridge between these incisions. Thus an additional mid-line skin incision is avoided in most patients who require a postoperative fistula repair procedure, without compromising the option of an extension for full mobilisation of the omental pedicle when this is necessary to ensure success.

INCREASING THE MIDLINE INCISIONAL ACCESS TO THE RETROPUBIC SPACE

A distal pre-pubic extension of the midline incision into the pre-pubic aponeurosis, and its reflection off the surface of the pubic bone, results in a remarkably effective increase in exposure of the retropubic space [1]. The access to the lower recesses of the retropubic space can be further increased by a partial resection of the pubic bone, but this additional exposure is rarely necessary in the female.

THE PROCEDURE FOR TRANSABDOMINAL VVF REPAIR

The transperitoneal supravesical approach provides the best exposure for the abdominal repair of a VVF. The traditional anterior transvesical approach for closing a VVF, originally described by Trendelenburg, provides a very limited exposure through which only a simple layered closure of a fistula is possible; this is no longer advocated for this purpose. To take advantage of the special features of this approach a PAPA position is essential to provide synchronous perineal access.

The patient is placed on the operating table in the perineo-abdominal position with an appropriate degree of head-down tilt to reduce venous pressure bleeding in the pelvis.

A mid-line abdominal incision is essential to enable the full length of the right gastro-epiploic pedicle of the omentum to be mobilised to support the fistula repair, if needed. For a simple fistula after hysterectomy, the initial lower mid-line incision may be made by the lower element of the suprapubic cross incision so that, when omental interposition support is required, it can usually be achieved using a simple horizontal Pfannenstiel-type skin incision with no need for an epigastric extension.

**TIPS AND TRICKS FOR THE SUPRAVESICAL REPAIR OF VVF**

1. A guiding finger in the vagina greatly facilitates the separation of the back of the bladder and the urethra from the vaginal wall at the margins of the fistula.

2. Bleeding deep in the pelvis is often controllable by simple vaginal finger-pressure while definitive haemostasis is being secured.

3. The exposure of the bladder base, the lateral paravesical space and the retrovesical/vaginal plane enables the ureter to be mobilised and re-implanted into the bladder by a reflux-preventing procedure when this is indicated, most commonly as a result of its involvement in the margin of the fistula.

4. When a vesical fistula extends down to or through the bladder neck, a definitive synchronous perineo-abdominal reconstruction of the sphincter mechanism can be achieved using a pre-vaginal abdomino-perineal tunnel. The separation of the urethra from the vagina is continued down to a peri-introital incision to create a pre-vaginal abdomino-perineal tunnel, 5–8 cm wide (three finger-breadths), to accept an effective bulk of omentum.

5. Omentum can be interposed using the supravesical abdominal approach alone, creating an intervening space for it by a downward and lateral extension of the separation of the bladder base and the urethra from the anterior vaginal wall of the vagina. The failure of an omental interposition repair should be a very unusual event; it is important to avoid three potential surgical shortcomings: (i) Inadequate size of the abdomino-perineal interposition tunnel, because this results in an insufficiency of the lateral tissue overlap. The omentum should not be used as a ‘simple plug.’ (ii) Failure to mobilise a sufficient bulk of omentum to fill the appropriately sized inter-position tunnel.

**USE OF A LATERALLY CURVED INCISION IN THE POSTERIOR WALL OF THE BLADDER**

If a vertical mid-line incision in the bladder is used to achieve a supravesical approach to a VVF it can be difficult, and sometimes impossible, to achieve side-to-side closure when the bladder wall and the lateral paravesical pelvic tissues are indurated (as they often are as a result of previous surgery, inflammatory fibrosis and especially after irradiation). It is generally advisable to curve the incision in the posterior wall of the bladder laterally because this creates an eccentric laterally based flap of the bladder wall that enables closure to be achieved by its simple rotation.

**THE OPERATIVE PROCEDURE FOR VESICO-VAGINO-RECTAL FISTULA REPAIR**

The procedure for a vesico-vagino-rectal fistula closure is an extended development of the abdomino-perineal closure of a complex VVF by omental interposition. A simple loop-ileostomy preliminary bowel diversion is preferred to a traditional loop colostomy, because it is easier for the surgeon to make, for the patient to manage and for the surgeon to close.

**POSTOPERATIVE CARE**

The patients have an occlusive wound dressing applied and are left with suprapubic and urethral catheters. All patients are continued on full antibiotic prophylaxis for 10 days, when a cystogram is taken, and provided that there is no leak from the bladder, the urethral catheter is removed and the suprapubic catheter clamped. Provided the patient is able to void without significant problems the suprapubic catheter is then removed. They are advised to avoid excessive activity for 4–6 weeks and then to gradually mobilise towards normal by 2–3 months.

**FROM SURGEON TO SURGEON**

We have tried to include helpful tips wherever possible as we have described these
techniques. In our experience, with a combination of self-retracting instruments, adequate exposure and good lighting, it is possible to close most VVF. Basic surgical principles of excising avascular tissue, avoiding 'dead space', creating tension-free anastomoses and draining urine, and where appropriate diverting the urinary stream, all combine to ensure a successful outcome.

The most surgically challenging situation; the so-called 'frozen pelvis'; this occasionally results from pelvic irradiation and is associated with an extensive fibrosis of the interstitial tissue that largely fills the pelvis. This is usually associated with extensive irradiation changes in the bladder, the ureters and the rectum. Sometimes after the treatment of a carcinoma of the cervix, there is a fistulating radio-necrotic cavity in the vaginal vault area. Traditionally, such a 'frozen pelvis' was treated by a double abdominal-surface urostomy and colostomy diversion, but this does not relieve the unfortunate patient of an offensive purulent discharge from a radio-necrotic cavity, the avascular walls of which are incapable of generating the proliferative granulation tissue required for its occlusive healing. The surgical resolution of a 'frozen pelvis' used to be widely regarded as an inoperable situation; however, after a subtotal exenteration that leaves the potentially salvageable elements in situ (the bladder base, the lower vagina and the anorectal mechanism) a functional reconstruction of some or all of these is often possible, especially if a sufficiency of transposable omentum is available, combined if necessary with a vaginoplasty to help fill 'dead space'.

In any patients with a fistula it is advisable to obtain support from a colleague with expertise in this area, as the closure of apparently simple VVF should be regarded as a specialist procedure. Often the surgeon who creates a fistula is not the one who is best qualified to repair it, although the temptation to attempt this may be great. From the patient's, the medical and the medicolegal perspectives, it is important that a postoperative fistula is repaired both expeditiously and successfully at the first attempt. The difficulty of fistula repair can escalate when the situation becomes complex but this should rarely be the result of a previous surgical failure.

REFERENCE


Correspondence: Christopher R. Chapple, Department of Urology, Sheffield Teaching Hospitals NHS Trust, Royal Hallamshire Hospital, Glossop Road, Sheffield S10 2JF, UK. e-mail c.r.chapple@sheffield.ac.uk

Abbreviations: VVF, vesico-vaginal fistula; PAPA, perineo-abdominal approach.
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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.

AIDS acquired immune deficiency syndrome
ANOVA analysis of variance
AUA American Urological Association
BAUS British Association of Urological Surgeons
BCG bacille Calmette-Guérin
BPH benign prostatic hyperplasia
BSA bovine serum albumin
BOO bladder outlet obstruction
CI confidence interval
CNS central nervous system
CT computed tomography
DMSA dimercapto-succinic acid
DRE digital rectal examination
DTCP diethylene-triamine-penta-acetic acid
EDTA ethylenediamine tetra-acetic acid
ELISA enzyme-linked immunosorbent assay
ESWL extracorporeal shock wave lithotripsy
FSH follicle-stimulating hormone
GFR glomerular filtration rate
GnRH gonadotrophin-releasing hormone
GP general practitioner
hCG human chorionic gonadotrophin
HIV human immunodeficiency virus
HPLC high-pressure liquid chromatography
ICS International Continence Society
IGF insulin-like growth factor
IgX immunoglobulin (class X, subclass \(\gamma\))
IPSS International Prostate Symptom Score
IVU intravenous urography
LHRH luteinizing hormone-releasing hormone
LUTS lower urinary tract symptoms
MAG mercapto-acetylglycine
MAG3 mercapto-acetyltriglycine
MHC major histocompatibility complex
MRI magnetic resonance imaging
NHS National Health Service
NSAIDs nonsteroidal anti-inflammatory drugs
PAGE polyacrylamide gel electrophoresis
PBS phosphate buffered saline
PCR polymerase chain reaction
PSA prostate-specific antigen
PTFE polytetrafluoroethylene
PUJ pelvi-ureteric junction
PUV posterior urethral valves
RCC renal cell carcinoma
SD standard deviation
SDS sodium dodecyl sulphate
SDF transforming growth factor
TCC transitional cell carcinoma
TNF tumour necrosis factor
TNM Tumour-Node-Metastasis
TRUS transrectal ultrasonography
TURP transurethral resection of the prostate
UTI Urinary tract infection
VUR vesico-ureteric reflux
WHO World Health Organization
<table>
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<tr>
<th>Month</th>
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| January | 4th International Symposium on Genitourinary Cancers, The Regent Beverly-Wilshire Hotel, Los Angeles, CA, USA. | Chairman: Nicholas J. Vogelzang, MD.  
 T +1 866 748 5140  
 F +1 928 962 4417  
 E cme@medidgms.com  
 W www.regonline.com/gucancers |
| January | Jackson Hole Urologic Conference  
Jackson Hole, WY, USA. | T +1 307 856 5758  
 W http://www.jacksonholeseminars.com |
| January | CSSAM/ISSAM North American Congress on The Aging Male in Vancouver, British Columbia, Canada. | Contact: Knes International 17, Rue du Cendrier, PO Box 1726 CH-1211 Geneva 1, Switzerland.  
 T +41 22 908 0488  
 F +41 22 732 2850  
 E aging@kenes.com  
 W http://www.kenes.com/aging |
| February | Educational Course in Urological Oncology. BAUS Section of Oncology Spring Meeting, Royal College of Physicians, Regent's Park, London, UK. | Contact: Jane Morrison, Sections Administrator, 35–43 Lincoln's Inn Fields, London WC2A 3PE, UK  
 T +44 20 7869 6950  
 F +44 20 7404 5048 |
| February | Urological Society of Australasia – Annual Scientific Meeting Melbourne, VIC, Australia. | Contact: Urological Society of Australasia  
 T +61 02 9362 8644  
 E lindy.moffat@surgeons.org  
 W http://www.urosoc.org.au |
| February | Mayo Clinic Rochester Department of Urology 2005 Annual Meeting  
Hapuna Beach Prince Hotel – Island of Hawaii, Kamuela, HI, USA. | Contact: W. J. Weiser & Associates, Inc.  
 T +1 847 517 7225  
 E sueo@wjweiser.com  
| March   | 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 19312, Saudi Arabia  
 T 966 3 844 0000 ext 4502  
 F 966 3 840 5936  
 E saudi17thurologyconference@hotmail.com or saudi17thurologyconference@yahoo.com |
| March   | 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 congressconsultants@uroweb.nl  
 W http://www.istanbul2005.org |
| April   | 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 |
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<th>Contact Information</th>
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<td>May 21–26</td>
<td>American Urological Association Annual Meeting, San Antonio, TX, USA.</td>
<td>T +1 800 908 9414 E <a href="mailto:convention@auanet.org">convention@auanet.org</a> W <a href="http://www.aua2005.org">http://www.aua2005.org</a></td>
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<td>June 11–16</td>
<td>Basic Sciences for Urology Residents, Charlotte, VA, USA.</td>
<td>T 800-282-7077 / 713-622-2700, ext 82 E <a href="mailto:meetings@houston.auanet">meetings@houston.auanet</a></td>
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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></td>
</tr>
<tr>
<td>March 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 Glasgow, UK.</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>
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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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