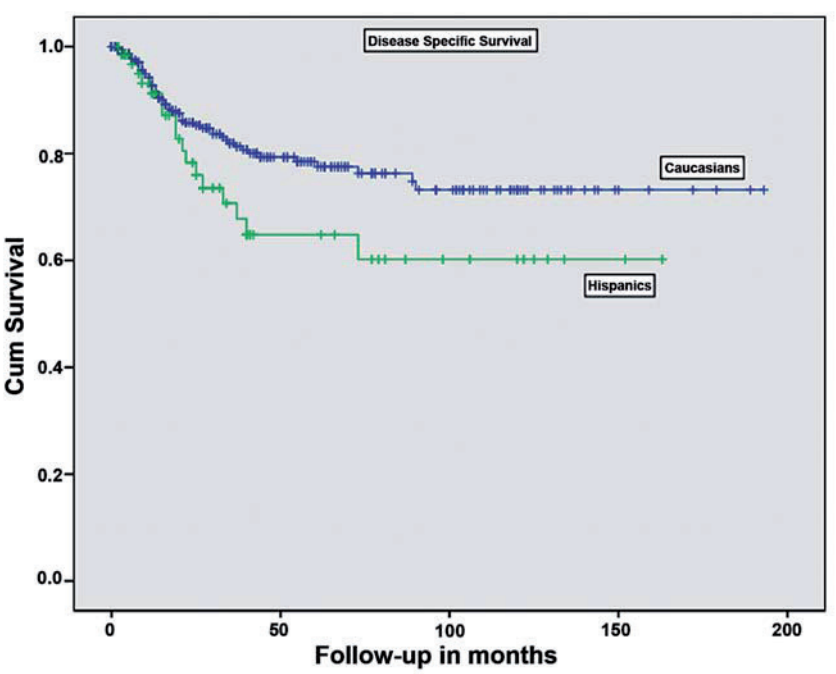
ISSN 1677-5538

International

Braz J Urol

Official Journal of the Brazilian Society of Urology
Official Journal of the Confederación Americana de Urologia
Official Journal of the Thai Urological Association
Volume 34, Number 6, November - December, 2008



Disease specific survival of patients submitted to radical cystectomy for bladder cancer (Page 695)

XXXI Brazilian Congress of Urology
November 7 - 11, 2009 - Goiânia - GO - Brazil

International Braz J Urol

EDITOR'S COMMENT

Cystectomy in Hispanics with Bladder Cancer

The November – December 2008 issue of the International Braz J Urol presents interesting contributions from many different countries, and as usual, the editor's comment highlights some papers.

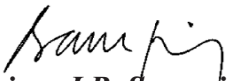
Doctor Manoharan and colleagues from University of Miami, Florida, USA, assessed on page 691 the presentation and outcome of patients undergoing radical cystectomy (RC) for bladder cancer. After studying 448 RC, 67 (17%) patients were categorized as Hispanic and the others as non-Hispanic. The authors found that Hispanics who undergo RC presented with higher stage disease, nevertheless, no significant difference in overall survival was observed. Doctor Ornellas, form National Cancer Institute, Brazil, provided an editorial comment on this paper.

Doctor Enayat and co-workers, from Sanandaj University, Iran, determined on page 699 the prevalence of asymptomatic urinary tract infection (AUTI) among pregnant women, as well as the antibacterial susceptibility of the isolates. Of 1505 pregnant women studied, 134 (8.9%) had bacteriuria. The authors found that Escherichia coli is the predominant organism, with 79 cases (58.96%), followed by CN Staphylococcus in 22 (16.8%). Most strains of Escherichia coli showed that they were resistant to ampicillin, tetracycline and gentamicin. Dr. K. Stamatiou, from University of Crete, Greece, Dr. Fiona Smaill, from McMaster University, Canada and Dr. Richard Colgan & Dr. Hengqi Zheng, from University of Maryland, USA, provided interesting editorial comments on this paper.

Doctor Sikiru and co-workers, form Jimma University, Ethiopia, investigated on page 708 the therapeutic efficacy of transcutaneous electrical nerve stimulation (TENS) in the symptomatic management of chronic prostatitis pain/chronic pelvic pain syndrome. Twenty-four patients diagnosed with chronic prostatitis- category IIIA and IIIB of the National Institute of Health Chronic Pain (NIH-CP) were referred for physiotherapy from the Urology department. Pre treatment pain level was assessed using the NIH-CP (pain domain) index. The TENS group received TENS treatment, 5 times per week for a period of 4 weeks (mean treatment frequency, intensity, pulse width and duration of 60Hz, 100μS, 25mA and 20 minutes respectively). The Analgesic group received no TENS treatment but continued analgesics; the Control group received no TENS and Analgesic but placebo. Post-treatment pain level was also assessed using NIH-CP pain index. The results revealed significant effect of TENS on chronic prostatitis pain ($p < 0.05$) and it was concluded that TENS is an effective means of non-invasive symptomatic management of chronic prostatitis pain. Dr. J. R. Yang, from Central South University, Changsha, China and Dr. Rodney U. Anderson, from Stanford University School of Medicine, California, USA, provided important editorial comments on this innovative manuscript.

Doctor Ferreira and associates, from University of Campinas, Brazil, evaluated on page 725 the effectiveness of the sentinel lymph node biopsy using lymphoscintigraphy in patients with penile cancer and at least one negative inguinal region. They studied 18 patients by biopsy of the sentinel lymph node from 32 negative inguinal regions and performed modified radical lymphadenectomy in these regions regardless of the biopsy results. The sentinel lymph node presented 0% false negative 66% sensitivity, and 79.3% specificity when compared with the modified inguinal lymphadenectomy as the gold standard treatment. The authors concluded that sentinel lymph node biopsy is a feasible method of assessing the presence of regional metastasis in patients with penile cancer and clinically negative inguinal regions. Dr. M. Tobias-Machado & Dr. Eduardo S. Starling, from ABC Medical School, SP, Brazil, Dr. Antonio A. Ornellas, from National Cancer Institute, RJ, Brazil and Dr. Philippe E. Spiess, from Moffitt Cancer Center, University South Florida, USA, provided interesting editorial comments on this manuscript.

Doctor Seseke and collaborators from Georg-August-University, Gottingen, Germany, assessed on page 715 the long-term outcome of patients with clinical stage I non-seminomatous germ cell testicular cancer (NSGCT I). The authors studied 52 patients and after orquiectomy, 39 patients were treated with chemotherapy, 7 patients underwent retroperitoneal lymph node dissection and 6 were managed with surveillance strategy. Tumor specific overall mortality was 3.8%. The mortality and relapse rate of the surveillance strategy, retroperitoneal lymph node dissection and chemotherapy was 16.7% / 50%, 14.3% / 14.3% and 0% / 2.5% respectively. The authors concluded that in case of doubt, adjuvant chemotherapy should be the treatment of choice, as it provides the lowest risk of relapse or tumor related death. Dr. S. D. Beck, from Indiana University, USA and Dr. Dalibor Ondrus, from St. Elisabeth Cancer Institute, Bratislava, Slovak Republic, provided editorial comments on this article.



Francisco J.B. Sampaio, M.D.
Editor-in-Chief

Review Article

International Braz J Urol Vol. 34 (6): 676-690, November - December, 2008

Localized Renal Cell Carcinoma Management: An Update

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ABSTRACT

Objective: To review the current modalities of treatment for localized renal cell carcinoma.
Materials and Methods: A literature search for keywords: renal cell carcinoma, radical nephrectomy, nephron sparing surgery, minimally invasive surgery, and cryoablation was performed for the years 2000 through 2008. The most relevant publications were examined.
Results: New epidemiologic data and current treatment of renal cancer were covered. Concerning the treatment of clinically localized disease, the literature supports the standardization of partial nephrectomy and laparoscopic approaches as therapeutic options with better functional results and oncologic success comparable to standard radical resection. Promising initial results are now available for minimally invasive therapies, such as cryotherapy and radiofrequency ablation. Active surveillance has been reported with acceptable results, including for those who are poor surgical candidates.
Conclusions: This review covers current advances in radical and conservative treatments of localized kidney cancer. The current status of nephron-sparing surgery, ablative therapies, and active surveillance based on natural history has resulted in great progress in the management of localized renal cell carcinoma.

Key words: *renal cell carcinoma; treatment; nephrectomy; surgical procedures; minimally invasive*
Int Braz J Urol. 2008; 34: 676-90

INTRODUCTION

Renal cell carcinoma (RCC) is the third most frequent urologic cancer and represents 2-3% of all adult malignancies. Adenocarcinoma is the most prevalent histologic subtype, responsible for approximately 85% of renal tumors (1). Historically, RCC was known as the tumor of multiple presentations due to the several signs and symptoms that could be present at the time of diagnosis. Currently, up to 40% of kidney neoplasms are detected incidentally because of the widespread use of imaging technologies (2). This has led to an apparent increase in the incidence of RCC (3).

For decades, radical nephrectomy was considered the gold standard treatment for localized RCC, representing the only curative option. Several open or laparoscopic approaches are now available. However, despite a small improvement in overall survival and good oncologic outcomes, radical surgery has a relapse rate that can reach 30% (4). Likewise, renal function outcomes can be poor, even in patients with a normal contralateral kidney. More recently, renal parenchyma preservation and nephron-sparing procedures are beginning to demonstrate satisfactory results, pointing toward a possible role of new minimally invasive energy-based ablation techniques in renal tumor therapy.

EPIDEMIOLOGY

World statistics show 208,000 new renal cell carcinoma cases/year and 102.000 deaths/year (1).

There is a geographical prevalence variation. The smallest incidence rates have been observed in Africa, Pacific Coast and Asia (except for Japanese men). In some countries, such as Denmark and Sweden the incidence has been decreasing for the last 20 years (5).

In Latin America, the highest incidence is observed in Uruguay and in the south of Brazil (Porto Alegre 10.2 per 100.000 men) (6), contrasting with low rates in the north of Brazil and in the middle-west area, Goiania for instance (7,8).

According to the American Cancer Society, more than 54,390 new cases and 13,010 deaths are expected in 2008 in the United States. Since 1950, the annual incidence has grown by 130%, at a rate of 3.7% (9).

Data from the U.S. Surveillance, Epidemiology and End-Results (SEER) study shows that 54% of renal tumors are organ confined at diagnosis, 20% are locally advanced and 25% of the patients already have disseminated disease. Approximately 50% of these patients will develop metastases. The 2-year survival rate for patients with untreated metastases is only 0-20% (10). In general, global survival rates at 5 and 10 years are 65% and 56%, respectively.

TREATMENT

The Trial Search Strategy

The computerized database of the US National Library of Medicine of the search engine PubMed (http://www.pubmed.gov), and the Latin American and Caribbean Health Sciences LILACS database were primarily searched for articles on localized renal cell carcinoma from 2000 to 2008. In an effort to identify the records, the search descriptors: "renal cell carcinoma", "kidney neoplasm", were combined with the following terms: "radical nephrectomy", "nephron sparing surgery", "minimally invasive surgery", "radio frequency", "active surveillance" and "cryoablation". The databases search was conducted from March to April 2008. These terms were crossed, resulting in vast number of papers. Among the abstracts we identified, papers were selected on the basis of their clinical relevance with respect to the aim of the review.

The introduction of radical nephrectomy as the standard of care, together with earlier diagnosis provided by an increased frequency of radiological imaging, has made some progress in RCC management. This has translated into a small, but significant better global survival (7). (Figure-1)

Radical Nephrectomy

Open Radical Nephrectomy

In 1882, Czerny performed the first radical nephrectomy. However, high sepsis and mortality rates delayed the popularity of nephrectomy. In 1969, Robson et al., published one of the most recognized and cited articles concerning the standardization of radical nephrectomy (11).

The choice of surgical access for radical nephrectomy is determined by the size and location of the tumor, patients' anatomy, and the surgeon's preferences. Whatever the choice of incision, the radical treatment should follow accepted oncologic principles. Contemporary series of open radical nephrectomies (ORN) report acceptable complication rates between 2-7%. The most common immediate complication is secondary hemorrhage (12).

Radical nephrectomy remains the most generally performed treatment for localized renal tumors. In clinical stage T3b tumors, radical nephrectomy with thrombectomy offers curative potential particularly in patients not exhibiting evidence of metastatic disease (13).

Laparoscopic Radical Nephrectomy

In 1990, Clayman accomplished the first laparoscopic radical nephrectomy (LRN) for a kidney tumor (14). After high initial costs and conquering the learning curve, Meraney and Gill concluded that this approach was 12% cheaper than open surgery (15). The well known benefits of laparoscopy have made this approach very attractive. Burgess et al. compared short outcomes of LRN and ORN and demonstrated less postoperative pain and an earlier return to normal activities (16).

Radical nephrectomies have been performed by laparoscopic approaches, emulating the open tech-

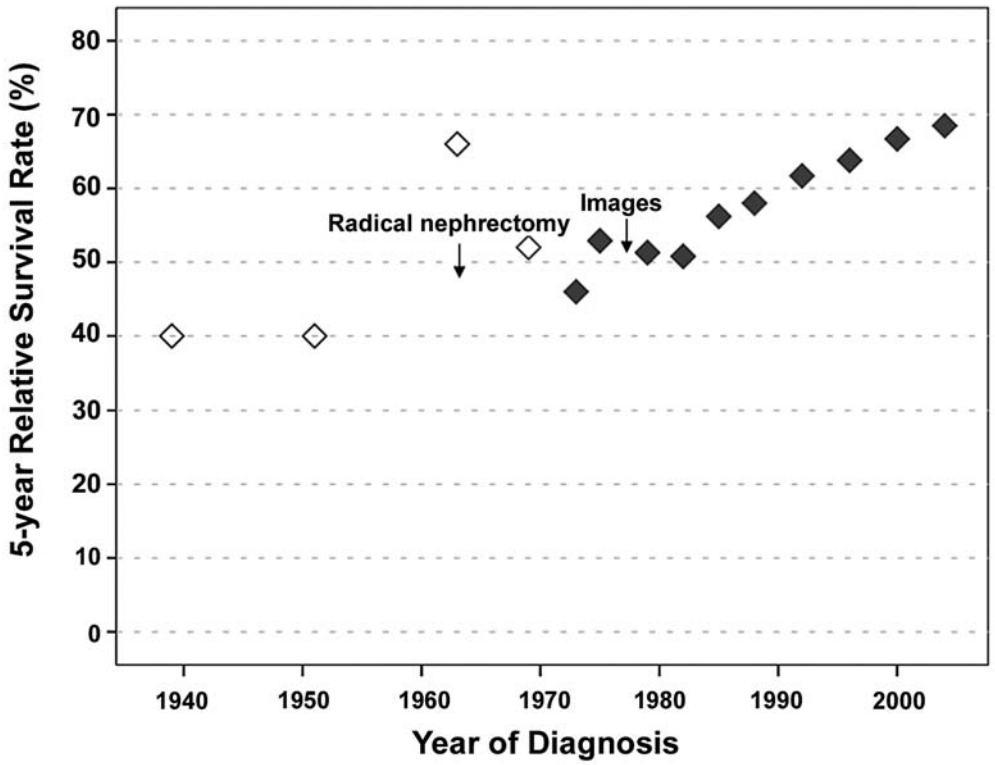

Figure 1 *– The observed 5-year relative survival rate of the kidney cancer patients and the historical facts responsible for a better rate of survival. Source: J Urol, 1969 ◊ (ref. 11); ♦ - SEER Cancer Statistics Review, 2006 (ref. 2).*

nique-with "en bloc" resection both feasible and desirable. Although it is possible to remove the specimen by morcellation, it impairs pathologic analysis and risks perforating the extractor bag. However, port site recurrences have been only rarely reported. Morcellation has been found to be a safe procedure, although contraindicated in patients with ascites (17).

Regarding long-term oncologic outcomes, several prospective cohorts compared laparoscopic versus open radical nephrectomy. Oncologic control after 3, 5, and 10 years of follow-up seems equivalent to open surgery (18-20).

LRN is an established standardized procedure for treatment of T1, T2 and some T3aN0 tumors. Nevertheless, despite some success of laparoscopy for more locally advanced tumors such as T3, open radical nephrectomy remains the gold-standard for these lesions (20). Today nephron sparing surgery is emerging as the new standard of care for small renal lesions (T1a and probably some T1b) (Table-1).

Adrenalectomy

Although ipsilateral adrenalectomy is feasible during radical nephrectomy, the real risk of adrenal invasion is low. Moreover, adrenal involvement can be detected preoperatively by computerized tomography or magnetic resonance image with a high sensitivity (21). However, false negative adrenal metastasis rate can be meaningful, particularly in upper pole masses and in the context of large renal masses. Direct tumor extension or metastatic involvement of the ipsilateral adrenal gland occurs in only 1.2-10% of surgical specimens. In a recent study, the adrenal involvement was found in 3.1% of 866 radical specimens (21). There are no reported prospective randomized studies examining the role of adrenalectomy in kidney cancer surgery. The low incidence of adrenal involvement and current imaging technology makes such a study unlikely.

Lymphadenectomy

Based on numerous published reports, such as: the UCLA experience and the EORTC 30881

***Table 1** – Indications for laparoscopic radical nephrectomy.*

Tumor < 4 cm, if it is not a candidate for partial nephrectomy
T1, T2-3a N0 and < 10-12 cm

randomized study, lymph node dissection is desirable only if preoperative imaging demonstrates enlarged lymph nodes. Lymph node involvement is associated with a poor prognosis although resection can increase survival when these patients are selected for adjuvant immunotherapy (22,23). Because there is no benefit in prospective oncologic outcomes, lymphadenectomy is considered unnecessary in unsuspected lymph node metastases as assessed by pre-operative imaging.

Partial Nephrectomy

Open Partial Nephrectomy (Nephron-Sparing Surgery - NSS)

The first partial nephrectomy was performed in 1870, by Simon, in a patient with hydronephrosis. The first oncologic partial nephrectomy was accomplished by Vizenz Czerny, successor of Simon in Heidelberg.

Today there is a debate about the accepted tumor size for partial nephrectomy. Patients with tumors of 4-7 cm with favorable anatomical characteristics are now treated conservatively (24). The complete removal of the tumor should be extended to have a negative margin. As regards the size of the normal parenchyma rim, some authors have reported that a macroscopic surgical margin of 0.5 cm is desirable, nonetheless the scientific literature supports that negative margin irrespective of size is adequate and safe (25). The survival data are excellent and 5-year cancer-specific survival is 90% (26). A retrospective analysis demonstrated a local recurrence rate of 7.5% (0-12%) (27). The partial nephrectomy is criticized for its higher complication rate, chance of local recurrence due to incomplete resection, and because some of these tumors can be multifocal. However, recent series report low rates of local recurrence, even in patients with positive surgical margins (27).

In patients with a solitary kidney, bilateral tumors, inadequate renal function or Von Hippel-Lindau disease (VHL), partial nephrectomy has mandatory indications to avoid dialysis and possible renal transplantation. In VHL disease, patients frequently have multifocal tumors and multiple premalignant cysts. In these cases, nephron-sparing surgery is postponed with the intention of delaying the onset of renal insufficiency. These lesions are resected when the tumor reaches a determined size (28).

In 2006, Huang et al. demonstrated that radical nephrectomy is a risk factor for development of chronic renal disease (glomerular filtration rate, GFR < 60 mL/min for 1.73m^2) when compared to patients undergoing partial nephrectomy (29). Studying a cohort of 662 patients, 171 had some degree of preoperative renal dysfunction, 50/287 and 142/204 patients developed CRD after partial and radical nephrectomy, respectively. The probability of not having chronic renal disease in 3 and 5 years was 80% and 67% in nephron-sparing surgery, respectively; and 35% and 23% in the radical surgery group ($p < 0.0001$). This functional result questions the role of radical nephrectomy, as the previous gold standard, in terms of best preserving long-term renal function for small cortical tumors (29,30).

There are no prospective clinical trials that demonstrate the long-term oncological results of nephron-sparing surgery. However, the first randomized prospective phase III trial was led by the Genito-urinary Group of the European Organization for Research and Treatment of Cancer (EORTC) in collaboration with groups in North America (EORTC 30904). Van Poppel et al., randomized 541 patients with tumors less than 5 cm and a normal contralateral kidney (partial nephrectomy PN = 268 and Radical nephrectomy RN = 273). They concluded that the complication rate with partial surgery is slightly greater than in the radical procedure. The oncological results are not yet available (31) (Table-2).

Therefore, based on functional long-term outcomes and similar retrospective oncologic endpoints compared to radical procedure, elective NSS an

***Table 2** – Indications for nephron-sparing nephrectomy.*

Formal Indications	
Benign disease suspicion	Bourneville syndrome
Bilateral tumors	Angiomyolipoma
Cystic nephroma	Familial RCC
Solitary kidney	Oncocytoma
Complex cyst	Graft kidney
Von Hippel-Lindau disease	
Relative Indications	
(probable future chronic renal disease or threatened contralateral kidney)	
Lithiasis	Vesicoureteral reflux
Arterial stenosis	Chronic pyelonephritis
Borderline renal function	Hypertension/diabetes
Elective Indication	
Tumor with a normal contra-lateral kidney	
Controversial Indication	
Large (T2), central, multifocal and non-familial tumors	

acceptable option for treat small RCC regardless of a higher complication rate. Nevertheless, the choice of invasiveness of the (laparoscopic or open) approach should not be considered the most important issue to select patients to radical or NSS procedures.

Laparoscopic Nephron-Sparing Nephrectomy

In some tertiary centers, the laparoscopic partial nephrectomy (LPN) is the standard technique for small cortical tumors (< 4 cm). Concerning the surgical technique, the vascular anatomy is very important (32). The polar nephrectomy is indicated in polar tumors as the wedge resection is indicated for central tumors (33). With this approach, the artery and the vein can be clamped when convenient even without cooling the kidney. Maintaining the kidney in warm ischemia enables a resection of up to 30 minutes (34). When complicated resections are anticipated, the hilum clamping is advised in conjunction with previous mannitol (12.5g) 20% administration and furosemide (10 mg) 5 to 10 minutes before clamping. Cooling the kidney with ice (for about 25 minutes lowering the temperature to 5-19º C) (35,36), helps prevent irreversible ischemic damage, thus making it possible longer resections up to 3 hours (37).

The most common complications of partial nephrectomy are hemorrhage (1.2-4.5%), urinary fistula (1.4-17.4%) and re-intervention (0-3.1%) (38,39). In the majority of cases, such complications can be managed conservatively, through endoluminal vascular or endourological techniques. The use of intraoperative ultrasound is a useful tool to evaluate depth and the presence of other tumors. Except in few centers, warm ischemia time is longer than in open surgery.

Permpongkosol et al. demonstrated that LPN has 5-year oncologic outcomes similar to open partial nephrectomy (40) (Table-3).

Even in modern series, there are heterogeneous populations between LPN and OPN, suggesting different indications. T1b tumors are more common in OPN than in LPN cohorts (41). Few studies report good initial results with hand-assisted technique and tele-robotic surgery (42).

Minimally Invasive Techniques

The minimally invasive techniques give new perspectives to the treatment of localized RCC, offering alternatives to conventional surgery. Currently,

***Table 3** – Published long-term outcomes for treatment of localized RCC regarding local recurrence, chronic renal disease (CRD) and cancer-specific survival.*

	Comparison	Number of Patients	Local Recurrence (%)	CRD (%)	5-year Cancer Specific Survival (%)
Dunn et al., 2000 (69)	ORN vs. LRN	33 vs. 61	-	-	92 vs. 90
Colombo et al., 2007 (19)	ORN vs. LRN	43 vs. 45	-	-	92 vs. 90
Hemal et al., 2007 (18)	ORN vs. LRN	71 vs. 41	0 vs. 0	-	94 vs. 95
Provet et al., 1991 (70)	OPN	52	2.0	-	88
Delakas et al., 2002 (71)	OPN	118	3.9	11	96
Fergany et al., 2000 (72)	OPN	107	10.3	51	88
Hafez et al., 1999 (73)	OPN	485	3.2	-	92
Becker et al., 2006 (74)	OPN (< 4 cm)	241	1.4	-	97 (10-years)
Becker et al., 2006 (75)	OPN (> 4 cm)	69	5.8	-	100 (10-years)
Lee et al., 2000 (76)	ORN vs. OPN	183 vs. 79	0 vs. 0	-	100 vs. 100
Leibovich et al., 2004 (77)	ORN vs. OPN	841 vs. 91	2 vs. 6	-	86 vs. 98
Patard et al., 2004 (25)	ORN vs. OPN	1075 vs. 379	6 vs. 2	-	94 vs. 97
Corman et al., 2000 (78)	ORN vs. OPN	1291 vs. 468	-	1.2 vs. 2.3	-
Huang et al., 2006 (29)	ORN vs. OPN	204 vs. 287	-	33 vs. 77	-
Dash et al., 2006 (79)	ORN vs. OPN	151 vs. 45	-	14 vs. 13	-
Lane et al., 2007 (66)	LPN	58	1.7	-	100
Permpongkosol et al., 2006 (40)	OPN vs. LPN	58 vs. 85	-	3.4 vs. 3.5	100 vs. 98
Gill et al., 2007 (80)	OPN vs. LPN	1029 vs. 771	-	1.5 vs. 1.4	99 vs. 99 (3-years)
Gill et al., 2005 (48)	Lap CRYO	56	3.5	-	98 (3-years)
Hegarty et al., 2006 (81)	Lap CRYO	60	6.7	-	100
Sewell P et al., 2005 (45)	Lap CRYO	103	10	-	97 (3-years)
Davol et al., 2007 (47)	Lap CRYO	48	12	-	100 (3-years)
Weld et al., 2007 (49)	Lap CRYO	81	1.2	-	100 (3-years)
McDougal et al., 2005 (54)	Percut RFA	16	-	-	100 (4-years)
Stern et al., 2007 (52)	PN vs. RFA	37 vs. 40	3 vs. 7	-	100 vs. 100 (3-years)

OPN = open partial nephrectomy; ORN = open radical nephrectomy; LPN = laparoscopic partial nephrectomy; LRN = laparoscopic radical nephrectomy; Lap CRYO = laparoscopic cryoablation; Percut RFA = percutaneous radio frequency ablation.

great interest exists in renal ablations by radio-frequency and cryotherapy. Frequently, those therapies are reserved for patients with serious co-morbidities. However, their low morbidity and ability to preserve renal parenchyma make them promising techniques.

Cryoablation

Hypothermic ablation therapy (-40° C) is performed through the introduction of a probe, whose function is to destroy the tissue by cellular damage from freezing, apoptosis, coagulation necrosis, and immunological action (43). The available devices use argon gas. Nonetheless, it is advisable that these procedures be properly guided by accurate imaging techniques. Some series have reported the safety of the technique, usually accomplished by laparoscopic or percutaneous means (Figure-2).

Hegarty et al., published a series of 164 cases treated by laparoscopic access. Forty-five of these

patients had a 6 year follow-up, with general and cancer-specific survivals of 80% and 98%, respectively. The local recurrence rate was 1.8% (44). There are no trials comparing long-term results of laparoscopic partial nephrectomy and laparoscopic cryoablation.

The percutaneous approach is even less invasive than laparoscopy and is able to be performed under local anesthesia and sedation. Sewell et al., studied 120 tumors treated by cryotherapy via percutaneous access with a cancer-specific survival of 97% and global survival of 90.2%. With 35.5 months of follow-up, the local recurrence rate was 10% and approximately one-third of patients needed more than one session (45).

In a recent review, a complication rate of 14% was observed in 139 procedures (4 laparoscopic and 16 percutaneous). The most frequent complications were perinephric hematomas requiring blood transfusion, hematuria, paresthesias and abscesses. Renal dysfunction occurred in only 1 of 139 patients (46).

Three year oncological results have reported a cancer-free survival up to 97% (47-49). It can be concluded that cryoablation, using two freeze/thaw cycles, is a safe therapy in small tumors in patients with comorbidities (47).

Long-term results comparing conventional open partial nephrectomy to cryotherapy are expected.

Radio Frequency Ablation

Hyperthermic ablation therapy by radio frequency elevates the temperature of the tissues above 100° C by reaching an impedance of 200Ω created by an electrical current. It is also performed by introduction of a probe, causing coagulation necrosis.

Short and intermediate-term results have demonstrated the safety and effectiveness of this method in small renal tumors. Follow-up of 27 months exists, and global and cancer-specific survival rates of 92.3% and 98.5% respectively were observed (50).

Stern et al., published their results in 37 ASA 1-2 patients. Only one patient had a local recurrence in a period over 2 years and he was treated by radical nephrectomy without recurrence after 1 year follow-up (51). The same author compared intermediate-term results of partial nephrectomy and radiofrequency ablation and concluded that 3-year oncological outcomes were similar (52).

Gervais and colleagues published a series of 85 patients with the treatment of 100 tumors percutaneously. One local recurrence was seen and there were eleven complications-such as 2 blood transfusions. Indeed, 100% of the tumors smaller than 3 cm achieved complete ablation while only 25% of tumors greater than 5 cm were treated completely (53). In another paper of the same group, a cohort of 16 patients was reported with the longest term follow-up available (4.6 years). Five patients died of unrelated causes and the 5-year cancer specific-survival was 100% (54).

Zagoria et al., obtained complete ablation (absence of contrast enhancement in the tumors on CT or MRI) in 116 of 125 tumors (93%) although residual tumors were observed in 30% of those larger than 3.7 cm in a follow-up of 13.8 months (55).

Centrally located tumors and those greater than 3 cm have been implicated as negative predictive factors for success. The observed complications are usually ureteral stenosis and urinomas. Residual tumors have been observed in nephrectomy specimens previously treated with radio-frequency ablation. There are concerns about viable tumor cells remaining after thermal ablation. However, such histological analyses were made in specimens previously treated with radiofrequency ablation just before the excision, therefore before complete coagulation necrosis had a chance to occur (56).

There are no systematic follow-up strategies after ablations of renal tumors. Usually, local recurrences or development of metastasis are assessed by images. The standard to define necrosis and response has been the absence of contrast enhancement in the lesion on post-treatment CT and MRI and not assessed by post-treatment serial biopsies. This arbitrary definition of radiographic success has been inadequate for determining complete ablation since positive biopsies have been reported in un-enhancing tumor beds (48). Therefore, current imaging techniques are quite limited to monitor and precise recurrences and repeated biopsies can be necessary to these purposes. Definitely, a more rigorous and uniform follow-up should be established, based on radiological findings and histological factors. Probably,

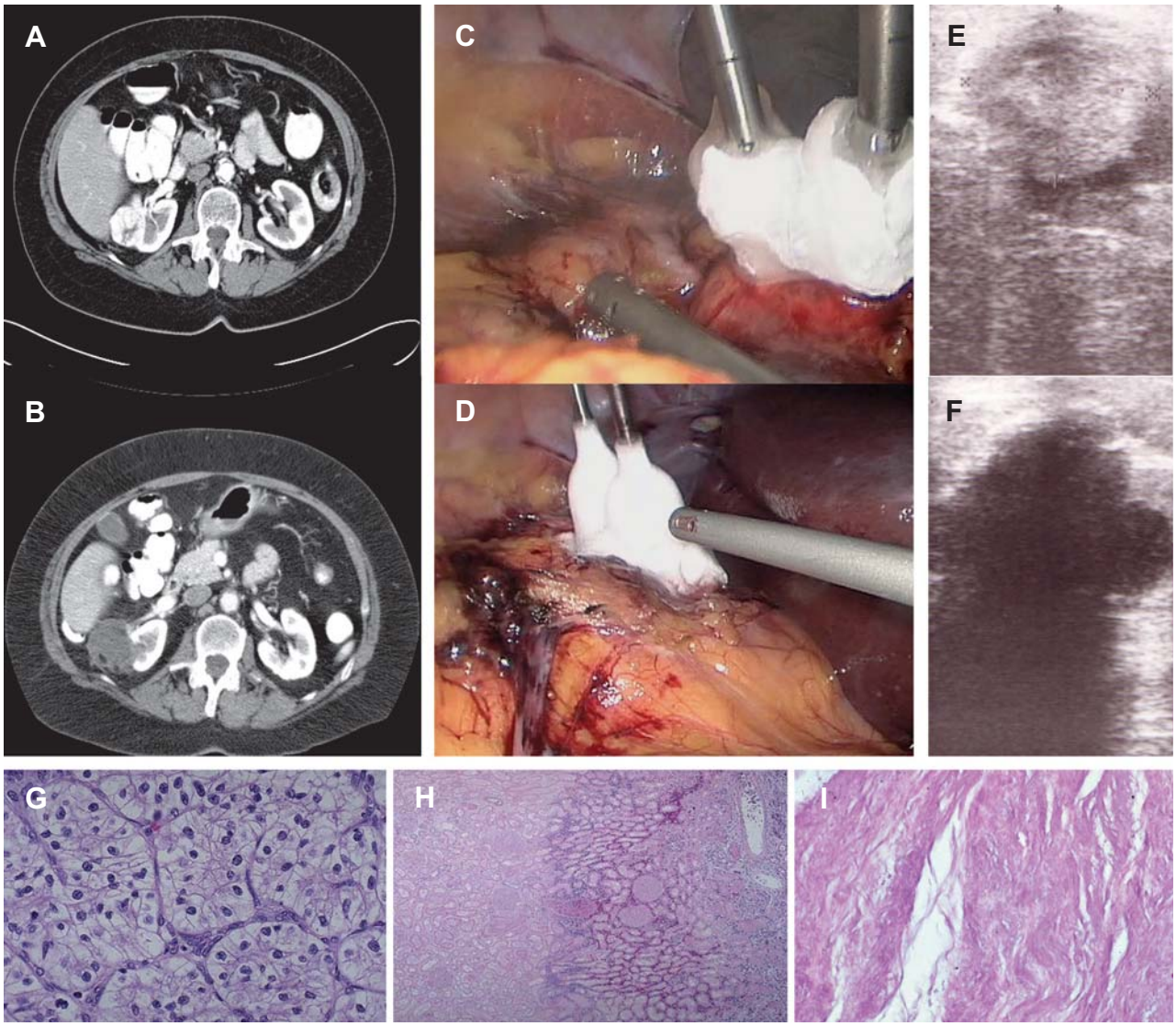

Figure 2 – *Renal cell carcinoma cryoablation. A) and B) Preoperative and six months post cryoablation CT images demonstrating absence of enhancement in the ablation site equivalent to the peripherical antero-lateral tumor in the right kidney. C) and D) Laparoscopic cryoablation of a renal tumor with cryocare® device (courtesy of Dr. Schwartz, Southern Illinois University). E) and F) Intraoperative ultrasound confirming the correct position of cryosensors and cryoprobes and monitoring the freezing procedure (ice-ball). Photomicrographies illustrating the renal cell carcinoma (G), an infarction area after cryotherapy (H) and fibrosis in a follow-up biopsy (I).*

in future, molecular markers will also be considered for this purpose. Ideally, surveillance after ablations as well as reporting of outcomes, technique and histological confirmation should be standardized to make possible comparisons of these ablative series with surgery.

Neo Adjuvant Therapy for Localized Renal Cancer

The role of neoadjuvant cytokines was investigated in patients with renal cancer undergoing radical nephrectomy. In a recent non-randomized controlled phase II trial, 120 consecutive patients

were allocated alternately to 2 groups: perioperative immunomodulation with subcutaneous Interleukin-2 in the week before surgery and control (57). The two groups had similar characteristics. Median follow-up was 40 months. The results revealed a difference in the tumor-specific 1-year and 5-year survival rates of 98% vs. 81% and 86% vs. 73% ($p = 0.04$) in treated vs. control groups. Despite this paper's non-randomized design, it signals a possible new approach in localized renal cell carcinoma. Future research in this field could be lead to the use of multi-targeted therapy as an option in selected patients with a high risk for recurrence.

Adjuvant Therapy for Localized RCC

Renal cell carcinoma expresses tumor antigens carbonic anhydrase IX and telomerase. Usually, these antigens promote an immune system response and eventually tumor destruction. These tumor antigens are available as potential targets for vaccination. Different mechanisms can make the tumor cells escape from immune surveillance. The cornerstone of tumor vaccination is to induce a tumor specific T-cell response.

Adjuvant tumor vaccination was reported in a randomized trial. A total of 553 patients were enrolled, comparing an autologous cancer cell vaccine. Jocham and colleagues have shown improvement in the 5-year progression-free survival for T2-3N0-3 tumors (58).

Randomized trials have shown no improvement in overall or disease-free survival with the adjuvant treatments radiotherapy, interferon, interleukin or BCG (58,59). The new targeted therapies are fast becoming the standard treatment for metastatic RCC. Nonetheless, it is not yet known whether adjuvant angiogenesis inhibitors are more effective than observation in treating locally advanced renal cell carcinoma. Several adjuvant trials for high risk localized RCC are recruiting patients to evaluate the role of adjuvant G250Ab, sunitinib and sorafenib versus observation after complete excision of unfavorable RCC (ASSURE, SORCE and S-TRAC trials) (60-62). Preliminary results concerning patient-reported outcomes and safety are not expected before 2010.

Active Surveillance

In spite of advances during the last decade, including a better understanding of tumor molecular biology, improved imaging, and minimally invasive procedures, approximately 30% of localized RCC will recur and progress. The current treatment framework considers that a better oncological outcome can be assured with early intervention. Hollingsworth et al., analyzing the SEER database that enrolled more than 34,500 tumors, concluded that the incidence of small tumors has increased (< 4 cm) and represents the largest increase in annual incidence of RCC. Similarly, surgical treatment has increased (63). Nevertheless, even with preclinical tumor detection and the treatment of incidental tumors, the overall mortality of RCC has not been impacted. Hence, current assumptions of treatment are being reviewed and new concepts of management have been created. Active surveillance is being proposed to treat some of these indolent tumors, but there are doubts regarding this indolence (64).

The tenets of surveillance propose that small renal masses (< 3.5 cm) with a slow annual growth rate (< 0.28 cm/year) can be observed and should not be promptly treated (63). Unfortunately, tumor stage and growth kinetics are not reliable factors to predict a tumor's natural history; in part because of the heterogeneous range of tumors considered here (65).

Investigations from the Mayo Clinic showed that 46% of tumors less than 1 cm were benign (66). Also, Gill reported a cohort where the median tumor size was 3 cm and 32% of these lesions were benign, the great majority was cancerous (67).

Recently, a meta-analysis confirmed that the growth rate was not significantly different between oncocytomas and RCC variants. Although rare, metastatic disease was observed in 3 patients (1%). Two of these patients became metastatic after the primary tumor reached 8 cm (54 and 111 months). Another patient had metastasis after a follow-up of 134 months. The pathological evaluation was provided in 131/286 (46%) lesions and 92% confirmed a malignant pattern (64). Although renal biopsy should not be performed in the majority of patients, more recent studies have reported less complications and better accuracy.

Active surveillance should be restricted to elderly patients with co-morbidities or patients that

refuse surgery. Thus, histological factors and molecular markers of progression are needed to improve the selection of patients for active surveillance.

Regardless of the approach, surgery remains the preferred standard of care for treating localized RCC. Complication rates of partial nephrectomies are not insignificant and ablative technologies are assuming a more prominent role. Recently, a meta-analysis compared oncological outcomes of these three strategies. Kunkle et al. analyzed 6,471 small renal masses described in 99 studies: 5,037 tumors were treated with nephron sparing surgery, 496 with cryoablation, 607 with radio frequency ablation and 331 were observed. The authors concluded that different groups have been treated by these strategies. This selection bias is clear when analyzing differences in tumor size, patient age, follow-up, and pathologic results. Although local control with ablation techniques has been inferior to nephron sparing surgery (radio-frequency 18-fold and cryotherapy 7-fold), no significant differences were found concerning metastatic progression, even with surveillance (68).

CONCLUSIONS

Surgery has been mostly responsible for the improvement in survival in localized renal cell carcinoma. Unfortunately, surgery for advanced localized disease (T3 and T4) remains unsatisfactory with high recurrence rates (20 to 30%). With a better understanding of the molecular basis of RCC the natural history can be predicted with improved accuracy, helping to identify high-risk tumors and establish targeted therapy for specific tumors.

Laparoscopic radical nephrectomy is the preferred treatment for localized renal masses (T1 and T2) deemed not amenable to partial nephrectomy (open or laparoscopic). The quality of life and preservation of renal function have now become important clinical issues. Therefore, attempts to achieve these goals have resulted in better clinical results and similar 10-year oncological outcomes for T1a lesions managed by partial nephrectomy, as well as T1b lesions (<7 cm) in favorable locations amenable to a partial nephrectomy..

Complete tumor resection must be advocated. Thus, all minimally invasive procedures should be compared to open surgery. Minimally invasive therapies, including cryosurgery and radio frequency ablation, by open, laparoscopic or percutaneous approaches are safe in patients with co-morbidities. The results obtained with minimally invasive therapies are promising. They are associated with a faster recovery, less pain, and decreased costs. However, long term oncologic efficacy remains to be demonstrated but is expected in the near future.

The role of other minimally invasive techniques, such as HIFU (high-intensity focused ultrasound), microwave thermotherapy, laser ablation, hypertonic solution instillation, and radio-surgery are uncertain and should at this time be considered experimental.

CONFLICT OF INTEREST

None declared.

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Accepted after revision:
September 3, 2008

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EDITORIAL COMMENT

In this review, the authors provide a comprehensive review of the current scientific literature on the management of localized renal tumors. The authors have adequately depicted that the management of small renal masses is no longer a simplistic discussion with patients that "the kidney needs to be removed" but rather that a spectrum of treatment choices are currently available from minimally invasive treatment modalities such as percutaneous radiofrequency ablation or cryotherapy, to nephron sparing surgery (laparoscopic, robotic assisted, open partial nephrectomy), extirpative surgery (laparoscopic or open radical nephrectomy), and active surveillance (for well-selected patients committed to a rigorous surveillance strategy and accepting of the potential risk of local, regional, and systemic progression).

One point that I would like to emphasize is that partial nephrectomy remains the "gold standard" approach for the management of localized renal masses deemed amenable to partial excision with negative surgical margins. The benefits of partial nephrectomy are increasingly being shown in terms of long-term renal function. The surgical approach used in performing a partial nephrectomy (i.e. open, pure laparoscopic, or robotic assisted laparoscopic) should depend on patient related, tumor specific, surgeon skill, and available hospital resources. The issue that is clear is that patient and case selection is of primordial importance.

Non-surgical, minimally invasive approaches to renal masses i.e. percutaneous cryotherapy or radiofrequency ablation are appealing to patients not ideally suited for aggressive surgical management and presenting with small renal masses amenable to this modality. Patients considering such minimally invasive approaches must be informed and accepting that long-term data on the effectiveness of these approaches are currently lacking and furthermore, patients must be committed to frequent radiologic imaging studies following the ablative procedure particularly within the first year (1,3,6,9, and 12 months). Patients must also be informed that a residual enhancing renal mass post-ablation may require repeated therapy (with either the same modality or another form of therapy).

What is clearly illustrated in the present discussion is that it is no longer appropriate for urologists to offer radical nephrectomy alone as the sole form of

treatment for a suspected localized renal mass. Patients must be educated and guided along this spectrum of currently available treatment armamentarium. With this knowledge at hand, patients are able to decide for themselves which modality is best suited for them. Furthermore, our knowledge is evolving and future discoveries and technological advances will impact our treatment options for a localized renal mass, our role will be to keep abreast of these advances and make them readily available to our patients.

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Clinical Urology

International Braz J Urol Vol. 34 (6): 691-698, November - December, 2008

Presentation and Outcome Following Radical Cystectomy in Hispanics with Bladder Cancer

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ABSTRACT

Objective: Significant racial and ethnic differences in the epidemiology of bladder cancer (BC) exist. Studies have shown African Americans to have lower incidence of bladder cancer than Caucasians, but higher incidence of invasive BC. Hispanics are the largest minority group in the United States. However, no reported studies on bladder cancer among Hispanics are available to date. As our center is in a unique position to study BC in Hispanic patients we were prompted to assess presentation and outcome of patients undergoing radical cystectomy (RC) for BC.

Materials and Methods: Between January 1992 and May 2006, 448 RC were performed. All relevant data were collected and entered into a database. Patients were categorized by ethnicity as Hispanic and non-Hispanic White. African-American and other minority groups were excluded because of the small number. Comparative analysis of Hispanic and non-Hispanic White patients was performed.

Results: 67 (17%) patients were Hispanic. Mean follow-up period was 41 (SD ± 40) months. Clinical and pathological data between these two groups were compared. Pre-cystectomy T stage was not significantly different between both groups. However, after RC incidence of ≤ T1 disease in Hispanics was lower (22%) than Caucasians (37%). This difference, statistically significant (P = 0.024) indicates that Hispanics who undergo RC present with higher stage disease. Kaplan-Meier log rank test indicated a difference in disease free survival and disease specific survival between the two groups but however it did not reach statistical significance (Log Rank P = 0.082, P = 0.063). No significant difference in overall survival was observed (P = 0.465).

Conclusions: Hispanic patients managed with RC for bladder carcinoma present with higher stage disease.

Key words: *bladder cancer; cystectomy; Hispanic; Latino*

Int Braz J Urol. 2008; 34: 691-8

INTRODUCTION

Bladder Cancer (BC) is the fifth most commonly diagnosed cancer in the United States. It is estimated that 67,160 men and women were diagnosed with BC and 13,750 died of this disease in the United States in 2007 (1). The prevalence of BC in the U.S. as of January 1, 2004 was approximately 511,790 (2). Radical cystectomy (RC) is an effective curative option for localized muscle invasive and high-grade urothelial cancer (3).

There is significant gender, geographic, ethnic and racial differences in the epidemiology of BC (4). Non-Hispanic White (NHW) men have the highest incidence of BC in the U.S. (40.5 per 100,000) (2). The incidence in African-American (AA) men was studied extensively and shown to be lower than the NHW (20.3 per 100,000) (2,5-7). Hispanic men have a similar incidence to AA men (20.2 per 100,000) and are about one-half the NHW rates. In women, the highest rates were in NHW (10.1 per 100,000). The AA and Hispanic women have an incidence of 7.6 and

5.5 BC per 100,000 women (2). The incidence is lowest in the Asian population. Although the incidence of BC in NHW population exceeds those of AA population, this trend was not observed as regards mortality (7). It has been reported that AA men and women with BC have higher disease specific mortality compared to the NHW (7,8). There are many reports available on the incidence, disease presentation and mortality of BC in AA and NHW population (8). However, the U.S. Hispanic population is a large and diverse ethnic group whose BC occurrence has not been well reported. Though marked differences among ethnic and racial groups with BC have been reported in the United States, to our knowledge no specific reports on BC in the Hispanic population is available to date (4,9,10).

The Hispanics are heterogeneous groups, which include Caribbean (Cubans, Dominicans and Puerto Ricans) Mexican, Central American and South American with other Latin American groups with Spanish ancestry. The term Hispanics refers to ethnicity rather than any particular race (2). Currently Hispanics are the largest minority group in the United States accounting for 13% (41 million) of the population. They are estimated to reach 47.8 million (15.5%) by the year 2010. From 1990 to 2000, the U.S. Hispanic population grew by 58%, while the total U.S. population grew by 13% (4). More than half of the Hispanic population in the U.S. lives in California, Texas, Florida, and New Mexico.

Miami-Dade County in Florida is the county in U.S. with the largest Hispanic population. Majority of this population with BC requiring radical cystectomy (RC) were treated at the University of Miami. This places our center in a unique position to study BC in Hispanic patients. In this study, our aim was to analyze and compare the presentation and outcome of bladder cancer in Hispanic patients who underwent RC.

MATERIALS AND METHODS

The study was approved by the Institutional Review Board. Between January 1992 and May 2006, 448 RC were performed by a single surgeon. All patients underwent radical cystectomy and bilateral pelvic lymph node dissection as a standard procedure. A retrospective chart review was completed. Demographic, clinical, and pathologic data were entered into a database. Patients were categorized by ethnicity as Hispanic, NHW, AA, and others. A comparative analysis of Hispanic and NHW patients was performed. AA and other minority group patients were excluded because of the small number in our series. Patients with unknown ethnicity and who underwent salvage cystectomy were also excluded from the analyses.

U.S. Census Bureau defines Hispanics as, are those people who speak Spanish as their first language and originated from the Spanish-speaking countries of Central or South America (11). All data on race and ethnicity was self reported. The chi-square and Student's-t-test were employed to study the difference among the ethnic groups. Kaplan-Meier log rank test was used to compare the rates of disease recurrence, overall and disease specific survival between the Hispanic and NHW groups.

RESULTS

A total of 448 RC were performed by a single surgical team between 1992 and 2006. Twenty-one (4.6%) salvage procedures and three (0.6%) patients with unknown ethnicity were excluded from the analysis. Twelve (2.7 %) AA and 12 (2.7 %) of other racial minorities were excluded from the analysis. This left 400 remaining patients in a study cohort of which, 333 (83%) were NHW and 67 (17%) Hispanics.

A comparative analysis was performed between 67 (17%) Hispanic patients and 333 (82%) NHW patients who met the inclusion criteria. The study cohort included 322 (81%) men and 78 (19%) women. The clinicopathological characteristics of the study groups are shown in Table-1. The Hispanic group was significantly younger than the NHW group. T stage at transurethral resection of bladder tumor (TURBT) was compared in both groups, no difference was found (P = 0.789; Table-2).

The distribution of pathological T and N stage at cystectomy were significantly different between the two groups. The incidence of muscle invasive BC was

Table 1 – *Descriptive details for the Hispanic and non-Hispanic white patients.*

Characteristics	Non-Hispanics White	Hispanic	p Value
Number (n)	333 (83)	67 (17)	
Gender (M:F)	4:1	3:1	0.315
Mean age at RC (years)	70	67	0.040
Mean follow-up (months)	42	39	0.668
Smokers	218 (65)	43 (64)	0.873
Neo-adjuvant chemotherapy	42 (12)	5 (7)	0.300
Pathological stage			
≤ T1	124 (38)	15 (22)	
T2	84 (25)	14 (21)	
T3	93 (28)	30 (45)	
T4	32 (9)	8 (12)	0.008
Node positive			
N1	25 (8)	2 (3)	
N2	41 (12)	16 (24)	0.026
Histological grade			
High	266 (80)	60 (90)	
Low	65 (20)	7 (10)	0.130
Recurrence	80 (24)	25 (37)	0.032
Adjuvant chemotherapy	56 (16)	17 (25)	0.118
Bacille Calmette-Guerin	115 (85)	20 (15)	0.459
Overall death	161 (48)	35 (52)	0.594
Disease specific death	54 (16)	17 (25)	0.081

Values are numbers and ( ) are percentage.

much higher at 78% in the Hispanic group compared with 63% in NHW group (P = 0.024; Table-3). In both groups interval between last TURBT date and cystectomy date were compared to identify any delay in performing RC, no difference was observed (P > 0.05).

The 5 year estimated overall, recurrence free and disease specific survival for the entire cohort was 50%, 62% and 76% respectively. The 5 year overall survival was not significantly different from the NHW group (P = 0.465; Figure-1). The recurrence free survival of the Hispanic group was significantly lower compared to the NHW group (P = 0.082; Figure-2). Similarly the 5 year disease specific survival of the Hispanic group was lower at 65% compared to 79% in the NHW group (P = 0.063; Figure-3). There was

Table 2 – *T stage before Radical Cystectomy in Hispanic and non-Hispanic white patients.*

Characteristics	Non-Hispanics White	Hispanic	p Value
Clinical stage			
≤ T1	92 (28)	21 (32)	
T2	240 (72)	45 (68)	0.550

Values are numbers and ( ) are percentages.

Table 3 *– Pathological T stage at Radical Cystectomy in Hispanic and non-Hispanic white patients.*

Characteristics	Non-Hispanics White	Hispanic	p Value
Pathological stage			
≤ T1	124 (37)	15 (23)	
T2,3,4	209 (63)	52 (78)	0.024

Values are numbers and ( ) are percentages.

no statistically significant difference in frequency of neoadjuvant and adjuvant chemotherapy administration among the study groups. In addition, instillation of Bacille Calmette-Guerin (BCG) vaccine was analyzed and no difference was found between both groups (P = 0.459).

COMMENTS

In 1999, the Institute of Medicine recommended that greater emphasis should be given to the ethnic groups, including cultural and behavioral attitudes rather than on biologic differences associated with race (12). Subsequently, several reports on the incidence and mortality of cancer among Hispanic men and women were published (4,9,10). These studies have shown significant variations in cancer incidence among different race and ethnicity. Hispanics had lower incidence of lung, breast and prostate cancers compared to NHW or AA. On the other hand, stomach and liver cancers were more common in Hispanics compared to NHW. Myeloma and cervical cancers were significantly more common in Hispanic women (4). These reports have clearly shown that the Hispanic population had an overall lower incidence of cancer than NHW or AA population (4,10).

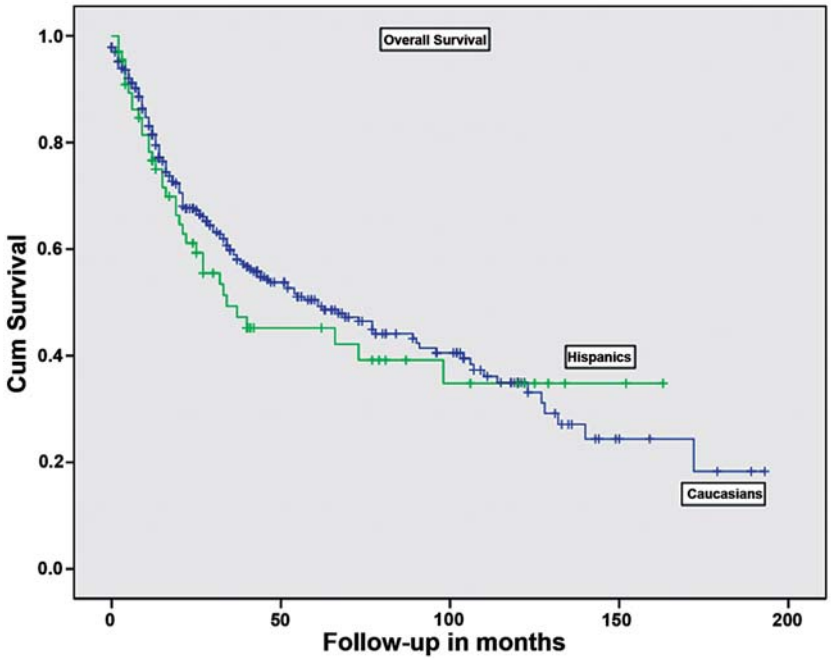

Figure 1 *– Overall survival.*

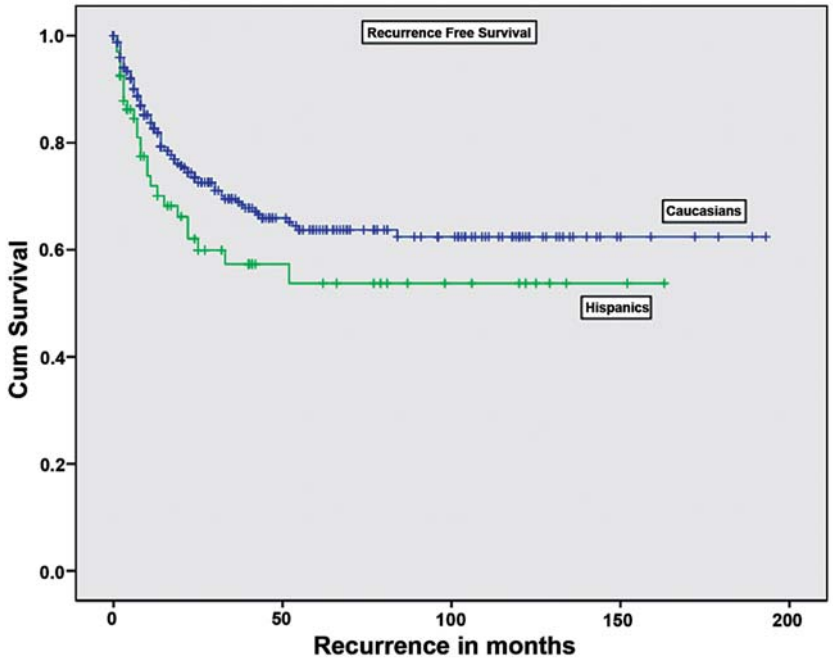

Figure 2 – *Recurrence-free survival.*

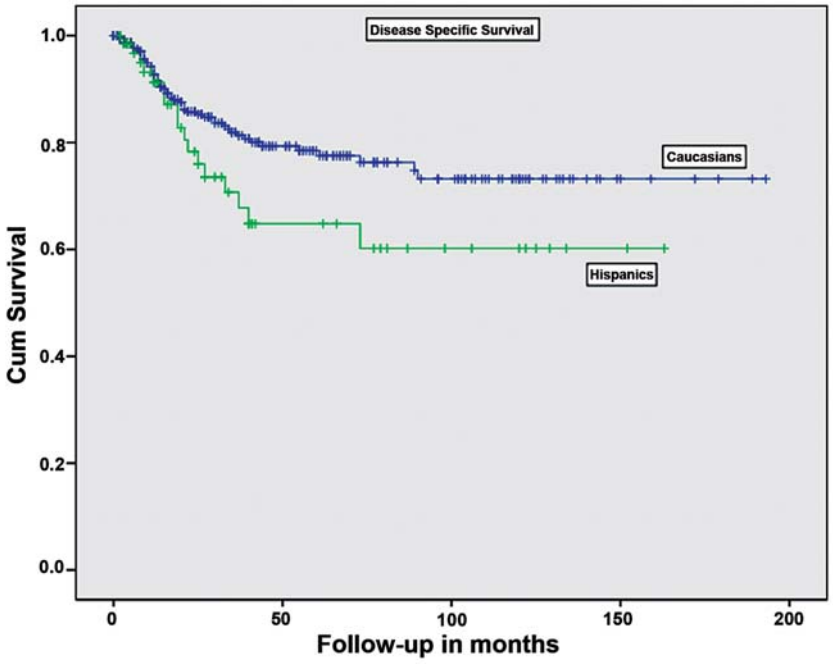

Figure 3 – *Disease-specific survival.*

In the U.S., BC is the fourth most common cancer of men in NHW and Hispanics. The exceptions are AA men and Asian Pacific Islanders where the BC is fifth and sixth most common cancer. In women, BC is the tenth most common cancer in NHW and ranked 13th in Hispanic, 14th in AA and 15th in API women (4).

Overall, Hispanic men and women had a lower incidence of BC. The standardized risk ratio for BC among Hispanic men was 0.74 compared to NHW men (10). However, our results showed that Hispanic men with BC tended to have a higher stage disease. The number of muscle invasive cancers (stage ≥ T2) was significantly higher in the Hispanic group. A total of 78% of Hispanic patients had muscle invasive cancers compared to 63% of NHW patients (P = 0.024). Similarly, lymph node involvement of cancer was higher at 27% in Hispanic patients compared to 20% in NHW patients. Moreover, 23% of Hispanic patients were staged N2 compared to 12% in NHW patients (P = 0.026). Similarly, more Hispanic patients received adjuvant chemotherapy compared to NHW patients; however, this was not statistically significant. Among the 34% of patients who received BCG treatment, no significance was in fact reached when comparing both groups.

Comparisons between clinical and pathological stage among both groups raised an important question; why are Hispanics presenting with more aggressive disease at radical cystectomy than NHW? When muscle-invasion before and after RC among ethnicities was analyzed, a difference was found in T stage. The possible explanations for these results might include first, incomplete resection before RC; second Hispanics may have more aggressive disease with faster tumor doubling time and/or; third, delays in the performance of RC might play a role in higher T stage at cystectomy. Our study showed no significance when the interval between last TURBT date and RC date were analyzed, possibly excluding the latter explanation.

In the Hispanic group, 37% patients had recurrences during the follow-up compared to 24% patients in NHW group. The Hispanic group had higher incidence of local recurrence (54%) compared to (43%) in NHW group (P = 0.355).

Similarly, the 5 year estimated disease specific and recurrence free survival was lower in the Hispanic group, close to statistical significance, which may well be achieved with more follow-up. The advanced T and N stage at RC may explain the poor survival outcome in these patients. Although, the 5 year overall survival of the Hispanic population (45%) was slightly lower compared to NHW patients (51%), the difference was not close to the level of statistical significance.

Studies have shown similar disease presentation among AA population and high mortality rate despite low incidence of BC. This difference in survival between AA and NHW populations was attributed to the fact that a larger proportion of NHW cancers are diagnosed at an early stage, and amenable to treatment. However, to date there has been no reported study suggesting higher stage presentation among the Hispanic population with BC.

We further examined the potential causes for higher stage disease among Hispanic patients at RC. Studies on migrated population have demonstrated that environmental factors dominate the epidemiology of many cancers. Wilkinson et al. showed that the overall cancer trends among men in south Florida reported a higher number of Hispanic men with cancers compared to NHW men during the period 1990-98. This study showed the proportion of Hispanic men who presented with cancer had increased nearly 20% between the past two decades. This change could be attributed to longer residence in the U.S. and presumably more acculturation. With the similar living environment, culture, food habits and exposure to known and unknown carcinogens may eventually equalize the cancer risk of Hispanics compared to that of native born NHW (10). However, we think the fastest growing Hispanic population in the south Florida could have influenced this outcome.

Smoking is a clear risk factor for the incidence and progression of BC. In our study, the smoking pattern was not different between the two ethnic groups. Factors such as cultural attitudes and beliefs were also attributed to be better predictors of advanced disease stage at the time of diagnosis (13). It has been reported that Hispanics fear cancer more than any other diagnosis (14). Socioeconomic status, access to cancer prevention and control services such as cancer screening and health education activities may contribute to differences in both incidence and

mortality. Many authors have cited cultural and language barriers as explanations for the advanced stage of cancer at the time of diagnosis for Hispanics and other minority groups compared with NHW group (10). The county poverty rate could be a useful indicator of the availability and accessibility to health services. Access to state of the art, quality cancer care is known to be unequal and to exacerbate existing disparities in cancer outcomes.

Several limitations of this study deserve mentioning. This is a retrospective study, which has its own limitations as regards applicability to the general population. Direct and self reporting of race/ ethnicity is preferred, however there are reports showing inconsistent reporting in medical records (15). We did not study the socioeconomic status and other issues such as access to the health care and the pattern of referral from primary care physicians. These could be potential confounding factors in this study.

CONCLUSION

The purpose of this preliminary study was to provide an overview of presentation and outcome of BC in Hispanic patients after RC. Hispanic patients are at higher risk of having higher stage disease at RC, compared to NHW. The disease specific survival of Hispanic patients after RC was lower compared to NHW. The rationale of these findings may be complex and multifactorial. However, this study showed a considerable difference in the presentation and outcome among the Hispanic patients. Further large population multicenter studies are necessary to validate this finding.

ACKNOWLEDGEMENTS

Financial support from “CURED 2007” and Mr. Vincent A. Rodriguez.

CONFLICT OF INTEREST

None declared

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Accepted after revision:
September 9, 2008

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EDITORIAL COMMENT

The authors present a retrospective study including 448 patients with bladder cancer submitted to radical cystectomy. This study examined patterns of invasive bladder cancer by ethnicity and gender. Unfortunately, the article does not discuss socioeconomic factors and other issues such as access to the health care and the pattern of referral from primary care physicians that could influence the indexes analyzed by the study. When the authors compared Hispanic and NHW patients concerning smoking and histological grade, the risks did not differ significantly, indicating that ethnic differences in bladder cancer incidence may not be related to smoking and grade. However, cancer risk may be highly dependent on the number of cigarettes smoked per day and we have not this information in the text. The Hispanic group had a higher incidence of local recurrence (54%) compared to (43%) in NHW group, although it did not reach statistical significance (P = 0.355). In this preliminary study, Hispanic patients are at greater risk of having higher stage disease at RC, compared to NHW and the disease specific survival of Hispanic patients after RC is lower compared to NHW. Evaluation of genetic differences between the 2 groups will need to be addressed in future studies.

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Clinical Urology

International Braz J Urol Vol. 34 (6): 699-707, November - December, 2008

Asymptomatic Bacteriuria among Pregnant Women Referred to Outpatient Clinics in Sanandaj, Iran

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ABSTRACT

Objectives: Determine the prevalence of asymptomatic urinary tract infection (AUTI) among pregnant women. We also determined the antibacterial susceptibility of the isolates to various antibiotics and associated risk factors in AUTI.
Materials and Methods: One thousand five hundred and five consecutive pregnant women were included in the study. Mid-stream urine specimen for complete examination of urine was obtained.
Results: Of 1505 pregnant women, 134 (8.9%) had bacteriuria. The mean age of the all the pregnant women included in the study was 28.40 years with a standard deviation of 6.16. Age ranged from 15 to 45 years of age. The urine culture of the asymptomatic pregnant women (1505 cases) showed growth in only 134 cases (8.9%). Escherichia coli was the commonest organism 79 (58.96%) followed by CN Staphylococcus 22 (16.8%) and S aureus 18 (13.43%).
Escherichia coli, which comprised 58.96% (79) of the isolates, were 88.62%, 87.35%, and 83.55% sensitive to cefotaxime, ciprofloxacin and cefotizoxime respectively. Similarly, E. coli were 89%, 70%, and 20% resistant to ampicillin, cotrimoxazole, and nitrofurantoin respectively (OR 1.57 95% CI 1.01, 2.44). After analyzing, four variables, hemoglobin levels seem to be independently associated with asymptomatic bacteriuria (OR = 9.41 (1.65-50.38).
Conclusion: Prevalence of asymptomatic bacteriuria among pregnant women was 8.9%. The predominant organisms were Escherichia coli 58.96% (79%), followed by CN Staphylococcus 22 (16.8%). Most strains of Escherichia coli showed that they were resistant to ampicillin, tetracycline and gentamicin.

Key words: *urinary tract infection; pregnant women; symptoms*
Int Braz J Urol. 2008; 34: 699-707

INTRODUCTION

Urinary tract infection (UTI) is one of the most common reasons for people to seek medical consultation and is also one of the most frequently occurring nosocomial infections. UTI affects all age groups, but women particularly pregnant women are more susceptible than men, due to pregnancy, short urethra, easy contamination of urinary tract with fecal flora and various other reasons (1,2).

Asymptomatic bacteriuria (ASB) is bacteriuria without apparent symptoms of urinary tract infections. The importance of ASB is a major risk factor for the development of UTI (3,4).

In the past years, scientists have spent considerable time and effort investigating the frequency of occurrence and consequences of asymptomatic bacteriuria in pregnancy (5-8).

Few studies in Iran have shown that the prevalence of asymptomatic bacteriuria among pregnant women ranged from 6.1 % to 10.9% (9-11).

Since isolated pathogens frequency and antimicrobial resistance rates can vary dramatically, even within the same countries, certain potentially resistant

strains such as those causing asymptomatic urinary tract infections (AUTI) among pregnant women, require surveillance of the most common causative species (12,13).

The prevalence rate of asymptomatic bacteriuria in pregnant women is comparable to the prevalence rate of non-pregnant women, indicating that pregnancy alone does not necessarily incline to the development of asymptomatic bacteriuria. It has been suggested that the frequency of bacteriuria increases by about 1% during pregnancy (6). The risk of acquiring bacteriuria increases with the duration of pregnancy from 0.8% of women with bacteriuria in the 12th gestational week to 2% at the end of pregnancy (6).

There are a number of conditions associated with an increased prevalence of asymptomatic bacteriuria in pregnancy. Low socioeconomic status, sickle cell traits, diabetes mellitus and grand multiparity have been reported; each is associated with two-fold increase in the rate of bacteriuria (5).

A major study comparing normal and high-risk pregnant women reported 6.0% prevalence in healthy women; 12.2% rate in diabetic women and 18.7% in women with a previous history of urinary tract infection (5). Maternal anemia has been reported to be associated with both asymptomatic bacteriuria and pyelonephritis, but an association with covert bacteriuria has not yet been confirmed (14).

There is insufficient local data on asymptomatic bacteriuria among pregnant women in Sanandaj. The objectives of this study was to determine the prevalence of asymptomatic bacteriuria detected on the first pre-natal visit among pregnant women and to identify factors that increases the risk of developing asymptomatic bacteriuria in pregnant women.

MATERIALS AND METHODS

A total of 10 clinics from South, North, West, East and Central of Sanandaj city were randomly selected for this study to determine the prevalence of asymptomatic urinary tract infection (AUTI) among pregnant women. We also determined the antibacterial susceptibility of the isolates to various antibiotics and associated risk factors in AUTI.

All pregnant women consulting for their first pre-natal check- up, who were willing to participate, were included in the study. The following patients were excluded (a) patients with history of fever (b) patients with any two of the following genitourinary complaints: dysuria, urinary hesitancy, urgency, slow stream, incontinence, frequency, incomplete voiding and (c) patients with any intake of antibiotics for any indication during the current pregnancy.

One thousand five hundred and five consecutive pregnant women were included in the study. Mid-stream urine specimen for complete examination of urine was obtained. Asymptomatic Bacteriuria in pregnancy is defined clinically as: (a) > 100,000 colony forming units of a single bacterial uropathogen per mL of midstream urine specimen and (b) the absence of symptoms attributable to urinary infection.

During the study period, all the urine samples were analyzed manually for culture and sensitivity using the semiquantitative calibrated loop method. Urine was inoculated on to blood agar and eosin methylene blue plates. The plates were incubated overnight. Next morning, a colony count was done, and interpreted according to our local interpretation guidelines. Bacteria were isolated and identified based on biochemical tests (15).

Antimicrobial susceptibility testing by disc diffusion was done according to the Clinical and Laboratory Standard Institute guidelines (16). This study was supported by grant from Kurdistan University of Medical Sciences.

Data was coded, computed and analyzed using SPSS version 11.5 and p values $\leq$ 0.05 were considered to be statistically significant.

RESULTS

Table-1 shows the demographic characteristics of pregnant women screened for asymptomatic bacteriuria. Of the 1505 pregnant women, 134 (8.9%) had bacteriuria. The mean age of the all the pregnant women included in the study was 28.40 years with a standard deviation of 6.16. Age ranged from 15 to 45 years of age.

Table 1 *– Demographic characteristics of pregnant women screened for asymptomatic bacteriuria.*

Characteristics	Non-Bacteriuria	Bacteriuria	p Value
Age (years)			
Mean (SD)	28.4 (6.16)	27.7 (6.0)	0.267
Range	16 - 45	15 - 41	
Pregnancy			
Mean (SD)	1.86 (0.95)	1.7 (1.0)	0.321
Range	0.0 - 8.0	1.0 - 8.0	
Parity			
Mean(SD)	0.74 (0.77)	0.65 (0.86)	0.292
Range	0.0 - 4.0	0.0 - 5.0	
Hemoglobin (g/dL)			
Mean(SD)	12.8 (6.3)	11.35 (1.5)	0.001
Range	7.8 - 13.7	4.6 - 21.2	

SD = standard deviation

Escherichia coli was the most common organism 79 (58.96%) followed by CN Staphylococcus 22 (16.8%) and S aureus 18 (13.43%) (Table-2).

Escherichia coli, which comprised 58.96% (79) of the isolates, were 88.62 %, 87.35%, and 83.55 % sensitive to cefotaxime, ciprofloxacin and cefotizoxime respectively (Table-3).

After analysis, four variables (age, parity, gravity, and hemoglobin level): hemoglobin levels seem to be independently associated with asymptomatic bacteriuria (OR = 9.41 (1.65-50.38).

COMMENTS

Women with asymptomatic bacteriuria during pregnancy are more likely to deliver premature or low-birth-weight infants and have a 20- to 30-fold increased risk of developing pyelonephritis during pregnancy compared with women without bacteriuria (17).

This study revealed that prevalence of ASB among pregnant women was 8.9%, which is similar to other reported studies, with minor differences (8,10,18).

Several studies have demonstrated that the geographical variability of pathogens occurrence in case of UTI is limited by the predominance of Gram negative, usually Enterobacteriaceae and particularly E. coli and Enterobacter spp., in various regions of the world and the resistance patterns of these organisms can vary significantly between hospital, countries and continents (19-22).

In this study the etiologic agent Escherichia coli 79 (58.96%) was the most frequent which is in agreement with similar reported studies in our region as well as in other parts of the world (3,8,10,20,21,23).

Gram-positive organisms have recently received more attention as causing bacteriuria and urinary tract infection. Although, they are seen in small numbers during pregnancy they are recognized as important causes of urinary tract infection. Our study findings of coagulase negative Staphylococcus

Table 2 *– Bacteriologic isolates from pregnant women with asymptomatic bacteriuria.*

Organism (s)	N (%)
E. coli	79 (58.96)
Coagulase negative Staphylococcus	22 (16.8)
Staphylococcus aureus	18 (13.43)
Enterobacter spp	10 (7.46)
Klebsiella spp	5 (3.73)
Total	134 (100)

Table 3 *– In vitro antibiotics sensitivity pattern of isolated organisms.*

Organism (s)	Cip	Ct	Nor	Sxt	Ctx	NA	Tet	Fm	Am	Gm	Amk
	Antibiotics Sensitivity (%)										
E. coli	69 (87.35)	66 (83.55)	58 (73.43)	20 (25.32)	70 (88.62)	15 (18.99)	01 (1.27)	23 (29.12)	02 (2.54)	04 (5.07)	07 (8.87)
CNS	14 (63.64)	12 (54.55)	10 (45.46)	04 (18.20)	18 (81.82)	16 (72.73)	02 (9.10)	10 (45.46)	08 (36.37)	ND	ND
S. aureus	06 (33.34)	ND	15 (83.34)	04 (22.23)	15 (83.34)	ND	04 (22.23)	08 (44.45)	06 (33.34)	ND	ND
Enterobacter sp	08 (80.00)	07 (70.00)	04 (40.00)	07 (70.00)	ND	09 (90.00)	04 (40.00)	06 (60.00)	04 (40.00)	07 (70.00)	04 (40.00)
Klebsiella sp	04 (80.00)	ND	ND	01 (20.00)	03 (60.00)	01 (20.00)	03 (60.00)	ND	03 (60.00)	03 (60.00)	02 (40.00)

Cip = ciprofloxacin; Ct = cefotizoxime; Nor = norfloxacin; Sxt = cotrimoxazole; Ctx = cefotaxime, NA = nalidixic acid; Tet = tetracycline; Fm = nitrofurantoin; Am = ampicillin, Gm = gentamicin, Amk = amikacin, ND = not done, CNS = coagulase negative Staphylococcus

(CNS) were the second most common urine isolate and are similar to the findings of Khattak et al. (23) and Abdullah et al. (24).

Regarding the antibiotics, E. coli exhibited 88.6 2% and 87.35% sensitivity to cefotaxime and ciprofloxacin respectively. In contrast, 73.43% and 79.74% were resistant to nalidixic acid and cotrimoxazole respectively and least susceptible to tetracycline, ampicillin, gentamicin and amikacin (Table-3). However, Shanson (25) reported the prevalence of resistance of urinary isolates to gentamicin was 2%.

In view of changing pattern of bacterial resistance to common drugs, the importance of educating physicians to use these antibiotics for empiric therapy is important.

Factors proposed to affect the frequency of bacteriuria during pregnancy include multiparity, age, previous medical history of UTI, diabetes mellitus, anatomic urinary tract abnormalities, and socio-economic status (3,13).

In this study, after analyzing, four variables such as age, hemoglobin, parity and gravity: hemoglobin levels hemoglobin levels seem to be independently associated with asymptomatic bacteriuria (OR = 9.41 (1.65-50.38) which is similar to other studies (5,13). Although the proposed association between covert bacteriuria and anemia during pregnancy has not been confirmed, nevertheless, our study found hemoglobin is to be an independent risk factor. In West Africa, anemia in pregnancy results from multiple causes, including iron and folate deficiency; malaria and hookworm infestation; infections, such as HIV; and hemoglobinopathies (26).

Few recently studies also revealed that anemia continues to be a major health problem in many developing countries and is associated with increased rates of maternal and perinatal mortality, premature delivery, low birth weight, and other adverse outcomes (27).

CONCLUSION

Prevalence of asymptomatic bacteriuria among pregnant women was 8.9%. The predominant organisms were Escherichia coli 58.96% (79)%, followed by CN Staphylococcus 22 (16.8%). Most strains of Escherichia coli showed resistant to ampicillin, tetracycline and gentamicin.

ACKNOWLEDGEMENTS

To Mrs. Kakaie S for reviewing the data coding and entry to computer. The Deanship of Scientific Research, Kurdistan University of Medical Sciences, provided financial support.

CONFLICT OF INTEREST

None declared.

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Accepted after revision:
September 1, 2008

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EDITORIAL COMMENT

Urinary tract infection (UTI) is one of the most frequently occurring nosocomial infections. UTI affects all age groups, but women particularly pregnant women are more susceptible than men, due to pregnancy, short urethra, easy contamination of urinary tract with fecal flora, immunodeficiency of the pregnancy and various other reasons. Several socio-demographic characteristics were found significantly associated with UTIs, such as age 30 years and more, illiterates and low educational level, low socio-economic level, unsatisfactory personal hygiene and use of underwear clothes other than cotton. Significant associations with UTIs were also found in multigravidae 4th and more, those having more than one child and those who previously suffered UTIs. Authors of the present study demonstrated that hemoglobin levels might be independently associated with asymptomatic bacteriuria. Further investigation may associate this finding with the low socio-economic level. Urological conditions in pregnancy represent a major diagnostic and therapeutic challenge. Asymptomatic bacteriuria and acute cystitis of pregnant women, even if uncomplicated and non-progressive are associated to poorer pregnancy prognosis and they need to be properly treated. Definition of the optimal antimicrobial agent for the treatment of asymptomatic bacteriuria or uncomplicated UTI in pregnant women is controversial. Among the most important factors in the choice of antimicrobial agent in a certain population of pregnant women to consider are the frequently isolated urinary pathogenic bacteria and microbial resistance. Until there are data from well-designed trials that establish the optimal duration of therapy for asymptomatic bacteriuria, standard treatment courses are recommended.

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EDITORIAL COMMENT

Screening for and treatment of asymptomatic bacteriuria is a standard procedure of obstetrical care and included in most antenatal guidelines. Untreated asymptomatic bacteriuria is a risk factor for pyelonephritis in pregnancy and associated with low birth weight infants (1). Screening for asymptomatic bacteriuria has been included as one of the most cost-effective strategies for maternal and neonatal health in developing countries in a detailed analysis of interventions to achieve the millennium development goals for health (2).

There are, however, difficulties in the widespread implementation of screening and treatment of asymptomatic bacteriuria. Educational programs should emphasize the importance of early antenatal care and healthcare providers need to be aware of the importance of asymptomatic bacteriuria. Facilities to culture the urine are often not available in under-resourced settings and alternative diagnostic tests that are less expensive, easier to implement and have been validated in these populations are urgently needed.

There is no clear consensus in the literature on either the duration of therapy or the choice of antibiotics and this study from the Kurdistan region of Iran confirms the importance of knowing local resistance patterns. The resistance to ampicillin and co-trimoxazole very high, but nitrofurantoin retained reasonable activity and most isolates were sensitive to ciprofloxacin. Where recent surveys of antibiotic susceptibility have been carried out, staggering rates of resistance to ampicillin and cotrimoxazole are often found, meaning that these less expensive antibiotics cannot be used for presumptive treatment unless antibiotic susceptibility testing of the organism can be routinely performed. For the women in this study, there are few oral alternatives available. While the organisms generally remained sensitive to one of the parenteral third generation cephalosporins, these agents are usually reserved to treat severe infections, and ciprofloxacin and the other quinolones are not usually recommended in pregnancy. Older agents, e.g. fosfomycin, may need to be reconsidered.

In this population, the prevalence of asymptomatic bacteriuria was within published ranges at 8.9%. Interestingly, staphylococcal species made up 30% of the isolates with 13% of urinary isolates reported as Staphylococcus aureus, an organism that has not traditionally been thought of as a urinary pathogen. The importance of the reported increase in gram positive organisms associated with bacteriuria in pregnancy is uncertain. More research which includes pregnancy outcomes and a thorough microbiology work-up, with speciation of the organisms and additional susceptibility testing is needed.

Enayat et al., did not provide information regarding the management of their patients and whether effective treatment was provided. Despite almost uniform guidelines, there is little evidence of adherence to screening recommendations. Poor adherence with screening in indigenous communities in Australia has been proposed as one explanation for worse pregnancy outcomes in this population (3). Structural problems related to the provision of care in remote communities were identified as contributing factors. It is important that well-designed treatment studies for women in low and middle income countries are performed that can address the emerging problem of antimicrobial resistance and additional research on the implementation and outcome of programs to screen and treat pregnant women for asymptomatic bacteriuria in diverse settings is needed.

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EDITORIAL COMMENT

In this edition of the International Braz J Urol authors Enayat, Fariba and Bahram report on their 2007 study of asymptomatic bacteriuria among pregnant women referred to outpatient's clinics in Sanandaj City, Iran. This is a well written, good study, on an important topic, handled in a scientifically rigorous manner.

The authors studied 1505 pregnant women from a total of ten clinics from South, North, West, East and Central portions of Sanandaj city, in the province of Kurdistan, Iran, in order to determine the prevalence of asymptomatic urinary tract infection. They found 8.9 % had bacteriuria. Although the prevalence of asymptomatic bacteriuria in pregnant women is similar to the prevalence in non-pregnant women, the consequences of not treating are much more severe in pregnant women. According to the IDSA Guidelines for the Diagnosis and Treatment of Asymptomatic Bacteriuria in Adults (1), the appropriate screening test is a urine culture early on in pregnancy, preferably at week 16 of gestation. Since pregnant women with asymptomatic bacteriuria have increased risk of developing pyelonephritis, premature delivery, and birthing infants with low birth weight, it is recommended to treat asymptomatic bacteriuria with antimicrobials. The microbes cited by the IDSA Guidelines paper include E. coli, Enterobacteriaceae, coagulase-negative staphylococci, Enteroccocus, Group B streptococci, and Gardnerella vaginalis. Although many microbes can cause asymptomatic bacteriuria, the most common uropathogen reported by this Guidelines committee and found in the study by Enayat et al. was E. coli, although at a lower percentage in the Iranian study.

Similar standards of care have been implemented throughout the world. The study by Enayat et al. extends the observations of asymptomatic bacteria among pregnant women into Sanandaj, Iran. The study further clarifies that the same microbes around the world have different resistance patterns in the Kurdistan city where there studied occurred. The materials and methods of the study are consistent with the scientific methods used in the IDSA guidelines. In the IDSA guidelines, positive screen is considered to be > 100,000 cfu/mL in a sample of urine that has been collected appropriately to minimize contamination from a person without symptoms of urinary infection. The study maintained the same clinical standards as they consulted pregnant women without symptoms of urinary infection during their first pre-natal check-up. The study discovered that E. coli was the most common (58.96% of pregnant women with asymptomatic bacteriuria), followed by coagulase negative Staphylococcus (16.8%), and Staphylococcus aureus (13.43%). However, the E. coli found was more resistant to the antibacterials that are recommended by the IDSA in their North American Guidelines. In Sanandaj, the E. coli were 89%, 70%, and 20% resistant to Ampicillin, Cotrimoxazole, and Nitrofurantoin respectively, while in North America, nitrofurantoin and sulfamethoxazole are prominently used to treat asymptomatic bacteriuria, because of the lower rates of resistance in the North American region. The study also indicated that E. coli in Sanandaj showed sensitivities to cefotaxime, ciprofloxacin, and cefotizoime at a rate of 88.62%, 87.355, and 83.55% respectively. Hence, it seems that E. coli in Iran tend to be more resistant to common antimicrobials and require more aggressive treatment options. Known factors in causing increased antimicrobial resistance are a greater use of a given antibiotic in the region, and the prevalence of clonal group A, for examples. However, the question of why resistance is higher among E. coli in Sanandaj remains unclear, and was not the objective of this paper.

This study highlights the need for communities to be aware of their own local patterns of antimicrobial resistance. Proper antimicrobial treatment of women with asymptomatic bacteriuria must take into account the prevalence of different uropathogens, with the knowledge of the efficacy of different antimicrobials for such populations. This study is particularly interesting because the authors have helped identify the patterns of resistance in their community and have provided sensitivity data, which will be of value to physicians in this area. On a global scale, it is important that each community also be aware of their local patterns of resistance so as to facilitate the proper prescribing of antimicrobials, when indicated.

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Clinical Urology

International Braz J Urol Vol. 34 (6): 708-714, November - December, 2008

Transcutaneous Electrical Nerve Stimulation (TENS) in the Symptomatic Management of Chronic Prostatitis/Chronic Pelvic Pain Syndrome: A Placebo-Control Randomized Trial

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ABSTRACT

Objective: The aim of the study was to investigate the therapeutic efficacy of transcutaneous electrical nerve stimulation (TENS) in the symptomatic management of chronic prostatitis pain/chronic pelvic pain syndrome.
Design: A pretest, posttest randomized double blind design was used in data collection.
Participant: Twenty-four patients diagnosed with chronic prostatitis- category IIIA and IIIB of the National Institute of Health Chronic Pain (NIH-CP) were referred for physiotherapy from the Urology department.
Intervention: Pre treatment pain level was assessed using the NIH-CP (pain domain) index. The TENS group received TENS treatment, 5 times per week for a period of 4 weeks (mean treatment frequency, intensity, pulse width and duration of 60Hz, 100μS, 25mA and 20 minutes respectively). The Analgesic group received no TENS treatment but continued analgesics; the Control group received no TENS and Analgesic but placebo. All subjects were placed on antibiotics throughout the treatment period.
Outcome measures: Post-treatment pain level was also assessed using NIH-CP pain index.
Result: Findings of the study revealed significant effect of TENS on chronic prostatitis pain at $p < 0.05$.
Conclusion: TENS is an effective means of non-invasive symptomatic management of chronic prostatitis pain.

Key words: *pain; TENS; chronic prostatitis; chronic pelvic pain*
Int Braz J Urol. 2008; 34: 708-14

INTRODUCTION

In 1995 the National Institutes of Health (NIH) classified prostatitis into 4 main categories: 1) acute bacterial; 2) chronic bacterial; 3) non-bacteria chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS); 4) asymptomatic inflammatory. The CP/CPPS was further subdivided into inflammatory (category IIIA) and non-inflammatory (category IIIB) prostatitis (1).

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), the subject of the present study is a debilitating condition diagnosed in the presence of chronic pelvic pain and lower urinary tract symptoms (2). CP/CPPS is the most common (3), yet most poorly understood "prostatitis syndrome" (4).CP/CPPS is truly a devastating disease.

A new perception of CP/CPPS appeared following the 1995 NIH/NIDDK workshop, which emphasized the importance of pain as the hallmark

of CP/CPPS and questioned the role of the prostate in producing the symptoms (2).

Chronic pelvic pain syndrome (NIH category III) and commonly manifests as pain in areas including the perineum, rectum, prostate, penis, testicles, and abdomen (5).The use of antibiotics in NIH category III is based on the uncertain etiology and the possibility that a potential pathogen or a cryptic non-culturable organism may be causative (6). Combination of analgesics, alpha-blockers (tamsulosin) antibiotics (TMP-SMX, fluoroquinolones or tetracycline), and muscle relaxants such as diazepam coupled with prostatic massage and supportive therapy (perineal support, pelvic floor physiotherapy, biofeedback and relaxation therapy) has been reported to yield higher cure rate and relief of pain and voiding symptoms compared to antibiotics alone and is the treatment option favored by most urologists (7).

However, no highly effective therapy has been identified. Thus far, strategies have focused on symptomatic relief (8). In addition, it is not clear whether therapy for IIIA and IIIB prostatitis syndromes should differ because the role of inflammation in these syndromes is incompletely understood (6).

Transcutaneous electrical nerve stimulation (TENS) was introduced as an alternatively therapy to pharmacological treatments for chronic pain. TENS currently is one of the most commonly used forms of electro analgesia. Hundreds of clinical reports exist concerning the use of TENS for various types of conditions such as low back pain, myofascial and arthritic pain, sympathetically mediated pain, neurogenic pain, visceral pain, and post-surgical pain (9-12).

The widespread use of TENS is useful for a wide range of chronic pain conditions (10,11). TENS is the application of pulsed square wave current through surface electrodes placed on the skin, to the peripheral nerve fibers for the control of pain (13). TENS is a non-invasive and non-addictive treatment (13). TENS does not produce anesthesia or nerve block (14).

Small uncontrolled studies have shown limited improvements in scores on the NIH Chronic Prostatitis Symptom Index with the use of biofeedback (15,16) and acupuncture (17). Physical therapies, including prostatic massage and sitz baths, have been recommended but have not been adequately studied.

The needs for the symptomatic management of pain in CP/CPPS with a non-invasive, non pharmacological, non-addictive technique such as TENS clearly exist. The purpose of the present study was therefore to determine the efficacy of TENS in the symptomatic management of CP/CPPS.

MATERIALS AND METHODS

Design - In this study, a double blind randomized pre-test, post-test independent placebo-control design was used.

Participants - The participants for this study included 24 diagnosed CP/CPPS patients attending the Urology Department of Murtala Mohammad Specialist Hospital (MMSH) and from private urologists. The inclusion criteria were randomly selected men between 24-50 years, previously diagnosed as category IIIA or IIIB CP/CPPS. Exclusion criteria were prostate and other urogenital cancer and infection, loss of skin sensation at and around painful area, cardiac pace maker, previous exposure to TENS and other electro analgesia.

Instrumentation -

1. TENS generated from ENS 931 (Enraf Nonius), Holland, with two conducting rubber electrodes and moist pads (size 3 cm X 6 cm).
2. TENS gel (Aquasonic gel) (J.J. Industry, Seoul, Korea).
3. NIH chronic prostatitis symptom index (NIH-CPSI) pain domain questionnaire.

Intervention - Those not on analgesic for at least one week and had not received any form of electromagnetic/acupuncture or heat therapy were recruited for the study. Informed consent was sought from subjects willing to participate in accordance with the ethics of human participation by the Ethical Committee of Murtala Mohammad Specialist Hospital, Kano. Pre treatment pain assessment was conducted by a neutral Assessor (Physiotherapist). NIH chronic prostatitis symptom index questionnaire, the pain domain describing the location, frequency and severity of pain was presented to each patient and instruction was given to indicate the pain characteristics and level by signifying a number on the scale. Subjects were then randomly assigned into three groups:

- X_1 (TENS group): Antibiotics + TENS only (n = 8)
- X_2 (Analgesic group): Antibiotics + Analgesic only (n = 8)
- X_3 (Control group): Antibiotics only + placebo tablets (n = 8)

Patients in the TENS group continued their antibiotics (ofloxacin) as prescribed by their Physician. The rationale for ofloxacin (300 mg t.d.s.) usage was because it is considered the recommended drug for chronic nonbacterial prostatitis management, covering culture-negative germs like Chlamydia (3).

For TENS application, patients were comfortably positioned based on the painful area (to cover the perineal-suprapubic region) for electrode placement. Sensory test was conducted on the skin over the painful area by using two test tubes with cold and warm water, also light touch via pin prick. It was ascertained that sensitivity of the area was intact, and that there was no resistance, this allowed for effective stimulation. TENS gel was applied on the surface of the electrodes to aid maximum transmission of current. Electrodes were placed on the skin overlying the painful area and held firmly in position as described by Radhakrishnan and Sluka (18); Oosterhof et al. (19).

The machine was switched on; a suitable and comfortable frequency and pulse width were selected on the stimulator by turning the appropriate knobs. Intensity knob was turned to a level when the patients felt a tingling or pins and needle sensation, the intensity was then reduced to a level that the patient reported a comfortable stimulation. Painful TENS was avoided.

Patients were stimulated with high TENS daily for an average of 20 minutes, mean frequency, pulse width and intensity of 100Hz, 100μs and 25mA respectively for a mean duration daily, 5 times per week for 4 consecutive weeks (average of 20 treatment sessions) (18-21).

The analgesic group continued with their antibiotics and analgesics (ibuprofen 400 mg b.d.); while the control group continued with their antibiotics (ofloxacin) and placebo tablets as prescribed by their physician for the same period. Seven days prior to their next medical consultation, after patients felt that they had exhausted their analgesic and TENS treatment was stopped (7 days post treatment [wash out period]).

Outcome measures - All subjects were assessed for the Post-treatment pain score using the same pre treatment procedure by the same neutral assessor who had no prior knowledge of the study, subjects' records or groups.

Data analysis - Mean and standard deviation (SD) were computed. Kruskal Wallis test and post hoc group differences were computed for the pre- and post-treatment pain values. Statistical analysis was performed on microcomputer using Statistical Package for the Social Sciences - SPSS (Windows Version 15.0, Chicago, IL.) A probability level of 0.05 or less was used to indicate statistical significance.

RESULTS

The age of subjects ranged from 24 to 50 years mean ± SD (38.17 ± 8.75), 23 to 55 years (45.38 ± 11.16) and 30 to 60 years (46.83 ± 8.16) for TENS (X_1), Analgesic (X_2) and Control (X_3) groups respectively.

The result of the present study indicated significant effect of TENS on chronic prostatitis pain. Table-1 shows the group mean and SD of pre

Table 1 *– Groups mean, SD and mean rank pre-test and post-test pain values (n = 24).*

		Pre-test		Post-test	
Variables	**N**	**Mean ± SD**	**Mean rank**	**Mean ± SD**	**Mean Rank**
TENS group pain	8	16.38 ± 2.88	10.00	9.00 ± 0.93	4.50
Analgesic group pain	8	17.13 ± 4.91	11.13	13.38 ± 1.50	13.38
Control group pain	8	20.25 ± 3.73	16.38	15.88 ± 1.55	19.63

Table 2 – *Kruskal Wallis summary for groups' pain level.*

Variables	N	Mean	SD	df	Chi-square	p Value
Pre-test pain	24	7.92	4.13	2	3.752	0.153
Post-test pain	24	2.75	3.17	2	18.804	0.000*

*$X^2_{(2.24)}$; p < 0.05; * significant; SD = standard deviation.*

and post-test pain values (levels). Table-2 shows the pretest-post-test mean, standard deviation and Kruskal Wallis analysis. Groups pain level did not differ significantly in the pretest pain values($X^2 = 3.752$ p = 0.153), while the post-test pain values differ significantly ($X^2 = 18.804$, p = 0.000).

Table-3 further showed a significant effect of TENS group over other groups at p < 0.05. Post hoc analysis indicated significant effect of TENS over analgesic (1 & 2 [K= 3.105]), placebo (1 & 3[K = 5.315]). Analgesic and placebo did not differ significantly (2 & 3 [K = 2.1746]).

COMMENTS

The purpose of the present study was to investigate the therapeutic efficacy of TENS in the symptomatic management of chronic pain in CP/CPPS. The result showed an appreciable effect of TENS in the symptomatic management of chronic pain in CP/CPPS. The predominant symptom of CP/CPPS is pain. Therefore, modalities to treat pain specifically may be effective. There is mounting evidence that the pain of CP/CPPS may be neuropathic and associated with central nervous system changes. The presence of central sensitization in patients with CP/CPPS was demonstrated by Yang and colleagues (22), who compared thermal algometry in men with CP/CPPS versus asymptomatic controls. Men with CP/CPPS reported a higher visual analog scale to short bursts of noxious heat stimuli to the perineum but no difference to the anterior thigh. Thus, these patients have altered sensation in the perineum compared with controls.

Many studies have investigated the effects of complementary and alternative medicine (CAM) strategies in the management of CP/CPPS. The result of the present study was in agreement with a similar non invasive CAM therapy, reported by Capidice et al. (23). In their pilot study, they investigated the effect of acupuncture in 10 men diagnosed as CP/CPPS (category IIIA or IIIB). Acupuncture was applied for 30 minutes, twice weekly for 6 weeks. They reported significant decrease in NIH-CPSI for pain and lower urinary tract symptoms and quality of life.

Another similar study was conducted by John and co-workers (24). Their study tested a high frequency, urethral-anal prototype stimulation device in men with CP/CPPS twice weekly for 5 weeks. The results demonstrated a significant decrease in the NIH-CPSI (P = 0.0002) with no urethral, anal complaints or other side effects The authors suggest that due to the positive results, simple technology and ability to be self-administered, this new device may be useful in the treatment of CP/CPPS.

Two similar studies (25,26) on non pharmacological, non invasive CAM therapy testing the value of biofeedback therapy for CP/CPPS yielded

Table 3 – *Post hock paired comparisons.*

	K1	K2	K3
Post pain KI	-	3.105*	5.315*
Post pain K2	3.105*	-	2.175
Pre pain K3	5.315*	2.175	-

*F (table value) = 2.89; p < 0.05; * significant.*

positive results. The first study assessed 62 patients who were refractory to conventional therapy (such as antibiotics and/or alpha-blockers) for greater than half a year. These patients were treated utilizing the Urostym Biofeedback equipment five times a week for 2 weeks with a stimulus intensity of 15-23 mA and duration of 20 min. The NIH-CPSI index noted a significant overall reduction in score ($P < 0.01$) and no side effects were reported during the trial (25).

A second pilot study evaluated biofeedback therapy in 19 men with pelvic floor tension and CP/CPPS. These results demonstrated significant improvement in pain scores as measured by the AUA symptom index ($P = 0.001$). While this study focused on testing the effect of biofeedback therapy in treating the symptoms associated with CP/CPPS, it also implicated the presence of pelvic floor tension contributing to pain and the paramount importance of muscular re-education for its treatment (26). These initial, positive biofeedback studies may warrant larger randomized clinical trials to confirm safety and efficacy as well as explore the mechanism of action of biofeedback therapy.

Many studies (9,11,12,27,28) have reported significant effect of TENS on visceral pain such as labor pain and dysmenorrhea. Based on this, TENS may be indicated in the management of chronic prostatitis pain; a similar visceral organ. Although there is no better way of eliminating pain than by removing its cause. With any symptomatic therapy, however, efficacy must be weighed with the risks involved. TENS might be preferable to large amount of analgesics and their side effects. Also, TENS is readily available to both patients and therapists, cheaper and easy to apply compared to other non invasive, non pharmacological complementary and alternative medicine therapies. Based on the result of the present study, the authors hereby concluded that TENS is an effective means of non-invasive, non pharmacological symptomatic management of chronic prostatitis pain.

Though, the present study indicated significant efficacy of TENS on chronic pain in CP/CPPS. However, there are some limitations of the study; they included the non availability of data on long term efficacy of TENS, few numbers of participants, non sham TENS group and failure to distinguished treatment between CP/CPPS category IIIA and IIIB. These limiting factors warrant more attention in future studies before a conclusive statement could be made. However, the present study could provide the relevant data in which future studies could base on.

ACKNOWLEDGMENT

The authors acknowledge the staff of the Department of Physiotherapy, Murtala Mohammed Specialist Hospital.

CONFLICT OF INTEREST

None declared.

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Accepted after revision:
August 28, 2008

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EDITORIAL COMMENT

Chronic prostatitis (CP) is one of the most prevalent conditions in urology, and represents an important international health problem. Throughout the past century, the diagnostic entity of CP has been recognized and its clinical characteristics well described. However, despite the multiple approaches to management of CP, no hard and fast guidelines have been developed.

The new perception of CP/Chronic Pelvic Pain Syndrome (CPPS) following the 1995 NIH/NIDDK workshop has emphasized the importance of pain as the hallmark of CP/CPPS. The authors investigated the therapeutic efficacy of transcutaneous electrical nerve stimulation (TENS) in the symptomatic management of CP/CPPS. This placebo-control randomized study show significant improvement in scores on the NIH-CP pain index with the use of TENS. Based on the present study, the authors concluded that TENS is an effective means of non-invasive, non pharmacological symptomatic management of chronic prostatitis pain. However, we still need more high quality multi-center randomized controlled trials from other countries and regions.

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EDITORIAL COMMENT

The authors are to be congratulated for an innovative approach to managing chronic pelvic pain syndrome in men, commonly referred to as chronic prostatitis. Multiple randomized placebo-controlled trials of oral pharmaceutical agents, including antibiotics, non-steroidal anti-inflammatory drugs, alpha blockers, and hormone blocking agents have been unsuccessful in ameliorating chronic pelvic pain symptoms. More local therapy is warranted. The need for symptomatic management of chronic prostatitis/chronic pelvic pain syndrome (CPPS) is certainly germane where no clear biological pathogenetic mechanism has been elucidated.

This approach to pain management needs verification with a sham treatment control. As with new surgical investigations that is a difficult clinical trial to devise. It is a stretch to describe this pilot trial as a double blind randomized placebo-controlled design. If we are to believe that neural dermatomes can act as pathways for counter-irritant stimulation that inhibits painful conception, then TENS is a good alternative. The endurance of a positive response to TENS needs to be assessed considerably longer than 4 weeks. Most treatment trials in chronic pelvic pain syndromes utilize a minimum 12-week observation period to endpoint.

Fortunately TENS application lends itself to patient controlled administration and intermittent personal selection of usage frequency. This is a huge advantage. It is akin to utilizing intermittent tibial nerve electrical neuromodulation for overactive bladder symptoms. Daily stimulation may not be necessary. In general, electrical neuromodulation applications continue to suggest avenues of pursuit that should be encouraged.

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Clinical Urology
International Braz J Urol Vol. 34 (6): 715-724, November - December, 2008

Long-term Clinical Outcome in Patients with Stage-I Nonseminomatous Germ Cell Cancer. A Critical Review of Own Treatment Modalities in a Retrospective Study

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ABSTRACT

Purpose: The optimal management of patients with clinical stage I non-seminomatous germ cell testicular cancer (NSGCT I) was considered controversial until the European Germ Cell Cancer Consensus Group determined unambiguous treatment strategies. In order to assess the long-term outcome we evaluated the data of patients with NSGCT I.
Materials and Methods: In a retrospective evaluation, we included 52 patients with a mean age of 26 years (range 15-58) who were treated with different modalities at our department between 1989 and 2003. Mean follow-up was 5.9 years (range 2-14 years). After orchiectomy, 39 patients were treated with chemotherapy, 7 patients underwent retroperitoneal lymph node dissection and 6 men were managed using a surveillance strategy. Survival, recurrence rate and time of recurrence were evaluated. The histological staging and treatment modality was related to the relapse.
Results: Tumor specific overall mortality was 3.8%. The mortality and relapse rate of the surveillance strategy, retroperitoneal lymph node dissection and chemotherapy was 16.7% / 50%, 14.3% / 14.3% and 0% / 2.5% respectively. All relapsed patients in the surveillance group as well as in the RPLND group had at least one risk factor for developing metastatic disease.
Conclusions: Following the European consensus on diagnosis and treatment of germ cell cancer in patients with NSGCT Stage I any treatment decision must be individually related to the patient according to prognostic factors and care capacity of the treating centre. In case of doubt, adjuvant chemotherapy should be the treatment of choice, as it provides the lowest risk of relapse or tumor related death.

Key words: *testis; testicular neoplasms; chemotherapy; surveillance; retroperitoneal lymph node dissection; outcomes assessment*
Int Braz J Urol. 2008; 34: 715-24

INTRODUCTION

The incidence of testicular cancer has increased over the last 50 years and is the most common malignancy in men in the 15-35 year age group. Nonseminomatous germ cell cancer occurs in slightly younger patients than in those with seminomas. Stage 1 disease is treated initially by orchiectomy, which assures accurate histological diagnosis. The importance of this pathological staging is reflected in the decision for the adjuvant treatment modalities. Although standardized recommendations for follow-up are not defined, patients without increased relapse risk such as vascular or lymphatic invasion, predominant component of embryonal carcinoma and undifferentiated elements (1), are recommended for

active surveillance. The relapse rate in this treatment strategy is approximately 30 %. Metastases will occur in the retroperitoneum in 54-78% and in the lung in 13-31% of the relapsed patients (2) and can be salvaged with cisplatin-based chemotherapy protocols (3). Following the recommendations of the European Germ Cell Cancer Consensus Group, in patients with reservations against the surveillance strategy, needing a high rate of compliance, adjuvant chemotherapy is the treatment of choice (relapse rate 3%). In case of reservations against the two afore mentioned options, nerve sparing retroperitoneal lymph node dissection (NS-RPLND) is suggested (3).

Vascular invasion is the most important prognostic indicator for developing metastatic disease in up to 48%. Patients with risk factors should be given two cycles of BEP (standard dose of cisplatin, etoposide, bleomycin) (3). However, cure rates of about 99% can be reached in patients with clinical stage I non-seminomatous germ cell testicular cancer (NSGCT I) with or without risk factors, independently of the treatment strategy.

Any decision for the optimal adjuvant treatment modality for non-seminomatous Stage 1 needs close co-operation between physician and patient to make sure, that the patient's compliance is in line with the chosen therapy. If a patient cannot deal with the psychological distress of a recurrence rate of approximately 30% (low risk) to 58% (high risk) (4) or if the compliance for regular follow- up intervals must be questioned, an adjuvant treatment should be preferred instead of the surveillance strategy.

In this study we retrospectively reviewed the patients with NSGCT I treated at our urological department from 1989 to 2003 to evaluate the long-term outcome. The results were compared with those obtained from other studies in the literature. Preferentially, we offered adjuvant chemotherapy with excellent cure rates, accepting an overtreatment in selected patients. The aim of this study was to critically review the applied treatment strategies with special emphasize on the relapsed patients.

MATERIALS AND METHODS

Patients - Between 1989 and 2003, 55 patients with NSGCT I were treated. Mean age was 26 years (range 15-58). Mean follow-up was 7.4 years (range 2-16 years).

Data acquisition - The records were reviewed for histological classification, clinical and pathological staging, serum tumor markers, adjuvant therapy and last follow-up.

Inclusion criteria - All patients had a histologically proven non-seminomatous germ cell cancer. Forty-three of the evaluated patients had a pT1 tumor, in 8 patients the histological work-up showed a pT2 stage and 1 patient had a pT3 tumor. Staging evaluations (chest X-ray, pre- and postoperative serum tumor markers, abdominal CT scan) excluded metastatic disease.

Therapy and follow-up - All patients had undergone radical orchiectomy. Following orchiectomy 39 patients were treated with chemotherapy of two (n = 29) or three (n = 5) courses of bleomycine, etoposide and cisplatin (BEP), or, in case of prior lung problems ifosfamide instead of bleomycin (n = 5). Seven patients underwent retroperitoneal lymph node dissection and 6 men were managed in a surveillance strategy. Follow-up evaluations included physical examination, chest radiographs, serum tumor markers, abdominal and testicular ultrasound and abdominal CT scan periodically as seen in Table-1. Patients were encouraged to be followed for at least 10 years.

Data evaluation - All patients with a documented follow-up of at least two years were included. Three men were lost to follow-up. The data of 52 patients could be evaluated based on a follow-up until June 2008. Evaluation included survival, recurrence-rate and time of recurrence. The previous histological staging and treatment modality was related to the relapse.

RESULTS

Up to the evaluation date three patients had died. One of these developed gastric cancer and died 9 years after treatment for non-seminomatous germ cell cancer. The initial histological workup showed a pT1 tumor and the patient was treated by retroperitoneal lymph node dissection (RPLND) after radical orchiectomy.

Table 1 *– Follow-up evaluations.*

Year	**1**				**2**				**3**		**4**		**5**		**> 5**
Month	3	6	9	12	15	18	21	24	30	36	42	48	54	60	Once a year
Physical examination	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Serum tumor markers	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Chest radiographs	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Ultrasound abdomen/testis	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
CT scan abdomen		x		x		x		x		x		x		x	

Two of the 52 patients (3.8%) died related to their underlying malignancy (Table-2).

As regards RPLND - Six patients from the RPLND group (n = 7) were disease free and well at the time of evaluation. Five of them had a pT1 and the other a pT2 tumor. The relapsed patient who had a pT1 tumor with teratoma and embryonal carcinoma was initially treated by orchiectomy. Subsequently an adjuvant modified RPLND was performed. Histological work-up did not show any pathologic lymph nodes. Twelve months after the diagnosis a recurrence occurred revealed by serum tumor markers. Initially, the patient refused further imaging and therapy. One year later, he had a CT scan showing a compression of the vena cava with a large retroperitoneal mass. Chemotherapeutic treatment (cisplatin, etoposide, ifosfamid) was started and a secondary RPLND was performed after completing this therapy. The histological workup revealed mature teratoma. Six months later elevated serum tumor markers again indicated tumor recurrence again. Because the CT scan did not show any pathology, biopsies of the remaining testis were performed that histologically showed only atrophic parenchyma without malignancy. However, another 2 months later the abdominal CT scan showed multiple liver metastases. A high dose chemotherapy (POMP-ACE: prednisone, vincristine, methotrexate, mercaptopurine, adriamycin, cyclophosphamide, etoposide) followed but tumor mass could not be downsized. The patient refused any further therapy and died of his disease a few months later.

Surveillance - Six of our patients entered a surveillance protocol. Three of them relapsed. Histological evaluation after orchiectomy had shown a pT 2 tumor with seminomatous and embryonal cell components in one of the relapsed patients. Despite regular follow-up, two years after primary diagnosis, retroperitoneal recurrence of the tumor was detected when the patient complained of flank pain and weight loss. Tumor markers were increased. At first, the patient refused any further imaging and therapy. After one year, the CT scan showed multiple metastases in the retroperitoneum and upper abdomen. Due to renal insuffiency a carboplatin (instead of cisplatin) based chemotherapy was initiated. Nevertheless, a few days later the patient died of complications caused by the chemotherapy with renal failure and tumor lysis syndrome.

Relapse of the tumor was recorded in another two patients (Table-2). The first patient had been managed in a surveillance strategy after orchiectomy for a pT1 tumor with components of embryonal carcinoma (predominant) and seminoma that relapsed at 11 years after initial treatment. Serum tumor markers were prominent in the follow-up. CT scan showed enlarged para-aortic lymph nodes. After chemotherapy treatment with cisplatin, etoposide and bleomycin he is

Table 2 *– Recurrences in the follow-up of 52 patients with NSGCT stage I.*

Pt. No.	Pathologic Stage, Histological Components	Adjuvant Therapy	Time to Recurrence	First Evidence for Relapse	Recurrence Site	Treatment	Results
1	pT1, teratoma, embryonal carcinoma	RPLND	12 month	serum tumor marker	retroperitoneum	chemotherapy, surgery	relapse after 6 month, refused therapy for 12 month, tumor bulk compressing the vena cava, chemotherapy, disease progressed, died
2	pT2, seminoma, embryonal carcinoma	surveillance	24 month		retroperitoneum	chemotherapy	refused therapy for 12 month, metastases retroperitoneum and upper abdomen, died during chemotherapy (tumor lysis with renal failure)
3	pT1, seminoma, embryonal carcinoma	surveillance	11 years	serum tumor marker	para-aortic lymph nodes	chemotherapy	disease free
4	pT2, yolc sac, embryonal carcinoma	surveillance	12 month	CT, serum tumor marker	interaortocaval lymph nodes	chemotherapy, surgery	disease free
5	pT1, embryonal carcinoma	BEP	24 month	serum tumor marker	retroperitoneum?	chemotherapy	disease free

disease-free up to now at a follow-up of 6 years since diagnosis.

The second patient presented with a large bulk of interaortocaval lymph node metastases and elevated serum tumor markers (AFP and ß-HCG) one year after primary diagnosis of a nonseminomatous germ cell tumor with components of yolk sac tumor and predominant embryonal carcinoma. The relapse was treated with three courses of bleomycin, etoposide, and cisplatin (BEP) and residual masses were

removed by secondary RPLND. Histological examination revealed mature teratoma tissue. Seven years postoperatively the patient remained disease free.

Chemotherapy – Thirty-nine patients underwent adjuvant chemotherapy after primary orchiectomy. One of them relapsed.

The contralateral biopsy of the patient performed at the time of orchiectomy of a pT1 tumor showed intratubular germ cell neoplasia (TIN). Radiation treatment of the remaining testis with a total dose of 20 Gy followed. One year later another biopsy of the testis did not show any malignancy. Another year later, serum tumor marker increased. The CT scan did not detect any pathologically enlarged lymph nodes. A further biopsy of the testis followed. The histological workup again showed a TIN. Assuming that it would be a generalized problem rather than a local tumor growth, the patient was treated with two courses of chemotherapy (BEP) and we included him in the recurrence group. He remained disease free at a follow-up of 5 years (Table-2, Pt. 5). Taken together, the incidence of TIN of the contralateral testis in our group of patients was 3% (1 of 33 biopsies, others refused biopsy or orchiectomy was performed in an external hospital without obtaining a biopsy). Our patient's cohort included 20 patients with one or more risk factors (embryonal carcinoma and/or vascular invasion) and 19 without.

COMMENTS

The incidence of testicular cancer has been increasing in recent years (5). The optimal management of these patients was considered controversial until the European Germ Cell Cancer Consensus Group primarily established clearly defined diagnostic and therapeutic strategies in 2004 and then updated in 2008 (3). Recommendations for active surveillance in patients with low recurrence risk (without evidence of vascular invasion, a predominant component of embryonal cell carcinoma or undifferentiated element) are uniformly accepted as long as the patients compliance is in line with the repeated diagnostic testing to detect relapses at an early stage (3,6). However, for patients who cannot manage the psychological distress of recurrence rates between 14% and 22 % (1) or those not candidates for surveillance for other reasons the adjuvant management remains controversial. Chemotherapy or retroperitoneal lymph node dissection (RPLND) are possible options. There is no consensus about, which strategy should be preferred. Krege et al. suggest chemotherapy with two cycles of BEP (3), whereas Stephenson and Sheinfeld prefer RPLND in these patients (6). In cases with a high risk of recurrence the same recommendation dilemma exists. Because of relapse rates up to 50%, most authors suggest an adjuvant treatment (7). However, some authors propose active surveillance even in this patients group (8).

The major advantage of the surveillance strategy is that up to 86% of the patients do not need any further treatment. Furthermore, relapses can be cured in nearly 100% of cases. However, the problem might be the patient's compliance and the psychological distress of the recurrence rates with a more intensive chemotherapy in case of relapse. A strict follow-up scheme and a compliant patient are mandatory otherwise an adjuvant treatment has to be recommended.

Advantages of RPLND over chemotherapy are the surgical removal of chemoresistant teratoma, as its biological potential is unpredictable, and, furthermore, the lower long-term toxicity (6). Relapses can be cured with chemotherapy in nearly all cases. Otherwise, patients will be exposed to surgery-associated side effects. The retrograde ejaculation with consecutive potential infertility based on surgical damage of the postganglionic sympathetic fibers (Th 12-L 3) forming the hypogastric plexus near the aortic bifurcation is an essential problem for young patients. However, even selective RPLND has significantly reduced but not eliminated ejaculatory problems (1).

The major disadvantage of adjuvant chemotherapy is potential overtreatment in up to 70% of unselected Stage I patients. Short-term side effects (Nausea, vomiting) can be managed with potent clinical agents and leucocytopeny and thrombozytopeny are usually mild. Long-term side effects are a possibly decreased fertility and the development of secondary malignancies, as seen in high dose chemotherapy with etoposide (9). Concerning fertility, it has to be considered that in patients with malignant germ cell tumors, semen quality of the unaffected contralateral testes is significantly worse than in the healthy male

(10) even before any chemotherapeutic treatment was applied. Furthermore, whether spermatogenesis is affected irreversibly by chemotherapy is determined by the cumulative dose of cisplatin. Pont and co-workers point out that the dose of even four courses of BEP is unlikely to cause any irreversible damage as the cisplatin dose generally remains below the critical dose of 400 mg/m^2 (11). Secondary malignancies are potentially caused by etoposide. The risk should be low because the critical dose is 1500-2000 mg/m^2 and the applied dose in adjuvant BEP will generally remain below (12). Furthermore, platin based therapy increases the risk of cardiovascular events (13). The above-mentioned studies only included patients with three or more courses and late effects seem to be dose dependant.

Considering these various factors, independently of the therapeutic regimen cure rates up to 99% (3) can be reached in patients with NSGCC. The decision about optimal adjuvant treatment after orchiectomy has to include risk factors as well as the patient's wishes and psychological situation and includes surveillance, adjuvant chemotherapy and RPLND.

To evaluate the outcome depending on the treatment strategies and risk factors of our own patients with NSGCT Stage I we retrospectively evaluated patients treated in our department between 1989 and 2003. Our preferred adjuvant modality was a chemotherapeutical treatment with two courses of BEP or ifosfamide instead of bleomycin in case of prior lung problems, accepting a potentially overtreatment in up to 50% of the cases but with very low recurrence rates (3). The minimal follow-up of the patients was defined as at least 2 years because the majority of relapses will occur within this period (14,15).

With respect to the low patient's number and the inhomogeneous group the cancer related mortality of the included 52 patients was 4% and comparable with the data obtained from the literature (16). All the patients relapsed in the retroperitoneum, independently from the chosen adjuvant modality.

Surveillance Group

Three out of six patients managed with a surveillance strategy after orchiectomy relapsed. Data published in the literature ranged from 30 - 75% (3,14,17) depending on risk factors. Whether adjuvant therapy was not recommended, or the patients primarily decided to active surveillance, or the concerned patients refused any further therapy, remains unclear from the retrospective evaluation of the records. However, all of our relapsed patients had one or two risk factors for developing metastatic disease, questioning the chosen strategy in these patients retrospectively. In two cases embryonal carcinoma was the dominating histological feature in the ablated testes in addition to vascular invasion of the tumor, including the patients retrospectively in the "high risk" group. The other patient did not have any vascular invasion but primarily rather embryonal carcinoma in the resected tumor. Time to recurrence was 1, 2 and 11 years, respectively. There was one tumor related death in these 6 patients on surveillance. At the point of recurrence, the respective patient foremost refused any further diagnosing and therapy (Table-2, Pt. 2), presuming that he did not show appropriate compliance to the primarily chosen surveillance strategy. In previous studies the rate was between 1, 2 and 2.8% (8,17). The high value in our group might be explained by the low number of patients included in this evaluation. After initiating an intensified chemotherapy one year after the metastatic spread the patient died because of chemotherapeutic induced side effects.

From the patients under surveillance which did not relapse one was "high risk" (embryonal carcinoma) and the other two were "low risk" cases (seminoma and embryonal carcinoma and seminoma, yolk sac tumor and embryonal carcinoma respectively, both with seminoma being the predominant component).

RPLND

Even though it is uncommon, one of our patients treated with RPLND after primary orchiectomy relapsed. Unfortunately, the patient refused any further imaging and therapy after suspicion of recurrence and the large retroperitoneal bulk made it difficult to evaluate the site of relapse. Therefore, it was impossible to assess whether it was an infield recurrence with lymphatic tissue left behind during the primary RPLND or an outside the border of the primary RPLND recurrence, as has also been described by other groups (18). The relapse rate after RPLND reported in the literature was between 5.8 - 21% (18,19). As seen from Table-2 (Pt. 1) the affected

patient, although showing a stage pT1, belonged to the high-risk group as the tumor showed embryonal carcinoma as predominating histological component. Although intensified chemotherapeutic treatment was initiated, the patient died of tumor progression.

Chemotherapy

One of the 39 patients (2.5%) treated with adjuvant chemotherapy relapsed. He suffered from a pT1 teratocarcinoma. Therefore, he initially did not have any risk factors for developing metastatic disease. Additionally, the histological workup showed a TIN of the contralateral testis. He was treated with two courses BEP and a radiation therapy was applied to the remaining testis. Two years later tumor marker increased but imaging did not show enlarged lymph nodes. Another therapy with two courses BEP was given. The patient has remained disease free to date. Comparably, formerly published studies showed a mortality of patients with NSGCT I treated with CTX between 0 and 4% (9,20,21). Relapse rates between 0 and 7% were reported (9,20,21). All these studies administered chemotherapeutic treatment only in high risk patients. Our patient cohort included 20 patients with one or more risk factors (embryonal carcinoma and/or vascular invasion) and 19 without. Retrospectively, most of the patients of the low-risk group were overtreated.

Limitations of the study - The indication for the particularly chosen treatment strategy could not be determined from the retrospectively assessed data. The reason for the inhomogeneous groups remains unclear and results in small numbers of patients especially in the surveillance and RPLND group. Small numbers can affect the reliability and confidentiality of results.

Rate is likely to be imprecise and the comparability of percentages is limited. Nevertheless, we attempted to include the data in this context and tied to discuss the results with respect to the low patient's number.

CONCLUSION AND CRITICAL REVIEW

The results of the evaluation of 52 own patients with NSGCT I treated with different adjuvant modalities were comparable with those obtained in the literature. All relapsed patients from the surveillance group had at least one risk factor for developing metastatic disease, presuming them to better candidates for adjuvant chemotherapy. One of these patients seemed to be fairly incompliant and was not a candidate for this follow up scheme retrospectively. Nevertheless, although the treatment strategies for our patients with NSGCT Stage I were highly inconsistent during the chosen observation period of 24 years, neither relapse rates nor mortality were mainly affected.

Considering all the factors involved, the decision for the correct adjuvant approach in patients with stage I nonseminomatous germ cell tumors should include risk factors for developing metastatic disease as well as patient related factors. Furthermore, individual clinical expertise should be considered in the decision. Summarizing the results in line with recent data from the literature, patients with NSGCT I should be treated following the recommendations of the European Germ Cell Cancer Consensus Group (3) avoiding an inhomogeneous therapeutic regimen and providing the optimal treatment for every single patient.

CONFLICT OF INTEREST

None declared.

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Accepted after revision:
August 14, 2008

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EDITORIAL COMMENT

Overall, the paper lacks strength due to the small number of patients in the RPLND and surveillance arms. In the introduction it is stated that "in patients with reservations to surveillance, adjuvant chemotherapy is the treatment of choice". In my opinion this is not true. Furthermore, in the discussion it states that "chemotherapy or RPLND are possible options". Overall there is not survival difference between any of the 3 modalities and RPLND is curable in high risk patients.

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EDITORIAL COMMENT

The introduction of cisplatin-based combination chemotherapy has revolutionized the treatment of metastatic testicular cancer. Owing to the high success rate in the salvage of disseminated cancer, it has become reasonable to argue for managing clinical Stage I nonseminomatous germ cell testicular tumors (CS I NSGCTT) patients with orchiectomy alone followed by surveillance. Patients, who relapse are treated with systemic chemotherapy, whereas those, who do not relapse, are spared unnecessary treatment.

The surveillance after orchiectomy alone has gained a lot of popularity in the management of CS I NSGCTT. Preliminary results were enthusiastic, but critical voices have been raised against general use of this option as a routine management. With longer observation, the relapse rate has been found to increase to 25 % or more after orchiectomy. Recent investigations have focused on determining the factors that identify a group of patients at high risk of the relapse, who might therefore benefit from a program other than surveillance.

The optimal management of CS I NSGCTT patients after an orchiectomy has been controversial for several decades, because of the difficulty of distinguishing true Stage I patients from those with occult retroperitoneal and distant metastases. Over the last 20 years, a surveillance strategy has been in practice at various centers to save patients in Stage I from unnecessary treatment-related morbidity. A number of primary tumor prognostic factors have been discovered that may be useful in stratifying CS I patients as to their likelihood of harboring occult disease. Up to 30 % of CS I NSGCTT patients have subclinical metastases and will relapse if surveillance alone is applied after orchiectomy.

The utility of vascular invasion (venous and lymphatic invasion) as a prognostic marker in CS I NSGCTT was first recognized in the 1980`s and during the years it became the main predictor of relapse in CS I NSGCTT managed by surveillance. Importance of embryonal carcinoma as a prognostic factor in low stage NSGCTT was discovered when surveillance studies were analyzed for relapse factors. Therefore, embryonal carcinoma is extremely important as a prognostic marker for occult disease in CS I NSGCTT. The presence of teratoma elements in testicular germ cell tumors has been known to have a favorable impact on prognosis. In contemporary era of prognostic factors in CS I NSGCTT, the presence of teratoma lessens the likelihood of occult disease. Teratomatous elements in the orchiectomy specimen predict for retroperitoneal teratoma, therefore primary RPLND in CS I NSGCTT patients was recommended for cases with the finding of teratoma in the primary

tumor. Patients can be stratified according to risk factors into different prognostic groups with different recurrence rates. According to EAU guidelines on testicular cancer and to reports of the European Germ Cell Cancer Consensus Group risk-adapted treatment is recommended as treatment of first choice in CS I NSGCTT patients, however, there is no worldwide consensus on the management of high-risk CS I NSGCTT. High risk patients, with vascular invasion are recommended to undergo adjuvant chemotherapy with two cycles of BEP regimen, intermediate risk patients are recommended to undergo primary RPLND and low risk patients, without vascular invasion are recommended to undergo surveillance.

It is generally accepted that surveillance is appropriate for patients with a low risk of relapse (without vascular invasion), however, there is no universally accepted standard protocol for surveillance of patients with CS I NSGCTT. The main advantage of surveillance being that 70-86 % of patients do not need any further treatment after orchiectomy. The disadvantages are the psychological and practical difficulties of intense follow-up for some patients.

The interesting article by Seseke et al. describes long-term experiences with CS I NSGCTT. Their information that vascular invasion is the most important prognostic indicator for a risk of developing metastatic disease is correct, but percentage up to 48% is too high. Also the results of the authors that patients managed with a surveillance strategy after orchiectomy showed a relapse rate 50 % is too high. Therefore, the results of authors are not comparable with those obtained in literature because of small number error causes (inhomogeneous number of patients treated by particular therapeutic modalities).

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Clinical Urology
International Braz J Urol Vol. 34 (6): 725-733, November - December, 2008

Sentinel Lymph Node Biopsy in Penile Cancer: A Comparative Study Using Modified Inguinal Dissection

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ABSTRACT

Introduction: In the case of clinically negative inguinal regions in penile cancer, the treatments proposed might vary from careful observation to radical dissection for all patients. We evaluated the effectiveness of the sentinel lymph node biopsy using lymphoscintigraphy in patients with penile cancer and at least one negative inguinal region.
Materials and Methods: In 18 patients, biopsy of the sentinel lymph node from the 32 negative inguinal regions and modified radical lymphadenectomy in these regions regardless of the biopsy results was performed. Clinical staging, pathological results of the sentinel and the other lymph nodes removed during lymphadenectomy, tumor behavior, local and inguinal recurrence and specific disease mortality were accessed.
Results: The mean age of the study sample was 57.7 years (44 - 81 years) and the sentinel lymph node presented 0% false negative 66% sensitivity, and 79.3% specificity when compared with the modified inguinal lymphadenectomy as the gold standard treatment.
Conclusion: Sentinel lymph node biopsy is a feasible method of assessing the presence of regional metastasis in patients with penile cancer and clinically negative inguinal regions. However, the optimal lymphoscintigraphy technique is still in evolution and requires further optimization at high volume centers.

Key words: *penile cancer; sentinel lymph node; inguinal; lymphoscintigraphy*
Int Braz J Urol. 2008; 34: 725-33

INTRODUCTION

While penile cancer is a rare disease in developed countries, its rate in underdeveloped countries is in fact the contrary (1). Disease treatment becomes a challenge when procedures related to prophylactic dissection of regional lymph nodes are evaluated.

When lymphatic metastasis in the inguinal region is clinically evident, classical radical lymph node dissection is the recommended treatment for improved overall survival and quality of life (1).

Lopes et al. comparing clinical and pathological features in penile cancer patients, found that the sensitivity, specificity, positive and negative predictive values, and effectiveness of clinical procedures for assessment of metastases were 66.7, 52.3, 60.8, 58.6 and 59.9%, respectively. On multivariate analysis of pathological factors only lymphatic ($p = 0.0008$) and venous ($p = 0.0410$) penile embolizations were significantly associated with risk of lymph node metastases (2).

In the case of clinically negative inguinal regions, the treatments proposed might vary from careful observation to radical dissection for all patients with intermediary solutions such as sentinel lymph node biopsy and modified dissection of the inguinal region with preservation of some structures and lymph nodes (3).

The principle of identifying the first drainage lymph node in the affected area and based on its

pathological assessment defining the need for more aggressive interventions seems to be an important and interesting procedure. This may be the reason why it has been the subject of several articles that demonstrate experience in this procedure or aim at assessing the validity of this test and its morbidity in relation to other interventions (4,5).

The purpose of our study is to evaluate the effectiveness of the sentinel lymph node biopsy using lymphoscintigraphy in patients with penile cancer and at least one negative inguinal region.

MATERIALS AND METHODS

A prospective study on 18 patients who had penile cancer and at least one clinically negative inguinal region was conducted between May 2000 and July 2005. This study was approved by Institutional Review Board.

All the patients, after signature of informed consent, had undergone partial penectomy, biopsy of the sentinel lymph node from the negative inguinal regions and modified radical lymphadenectomy as proposed by Catalona (1988) in these regions regardless of the biopsy results (3).

Biopsy of the sentinel lymph node and classical radical lymphadenectomy were performed in the positive inguinal regions.

Patients were classified according to surgical staging and histological level based on the TNM 2002 system proposed by the UICC/AJCC (6).

Patients underwent lymphoscintigraphy with ^{99m}technetium-labelled nanocolloid, which was injected intradermally around the tumor or into the distal penile shaft skin.

Four hours later, the sentinel lymph node was identified during surgery using a hand-held γ-probe. Complementary methods such as the peri lesion methylene blue injection were not used in this protocol.

Data assessment included clinical staging, pathological results of the sentinel lymph node and the other lymph nodes removed during modified lymphadenectomy as well as post-surgical tumor behavior, verifying local and inguinal recurrence and specific disease mortality.

RESULTS

The mean age of the study sample was 57.7 years (44 - 81 years) and the initial clinical assessment revealed that four patients had a positive inguinal region, which left 32 inguinal regions to be studied using the proposed method as clinically affected regions were excluded from the study.

In 6 of the 32 inguinal regions studied, the lymphoscintigraphy did not detect the sentinel lymph node when the gamma camera and the intraoperative portable probe were used, which meant that 26 inguinal regions with sentinel lymph nodes were identified and a total of 52 lymph nodes were removed at this stage. It should be underscored that one of the six undetected lymph node inguinal regions was in a patient with a clinically contralateral positive inguinal region.

The results of the pathological study of the sentinel lymph nodes revealed that only two inguinal regions of the 26 regions studied were affected (7.7%).

It should be emphasized that of these two clinically negative regions with positive sentinel lymph nodes, one of them was in a patient with a clinically positive contralateral inguinal region.

When the pathological study results of the modified lymph node dissection specimens in 32 clinically negative inguinal regions were assessed, three were found to be positive. The positive result indicated the need for radical procedure.

Two of them were from inguinal regions with positive sentinel lymph nodes and one was found among the six clinically negative inguinal regions without sentinel lymph node detection. Furthermore, one of the two positive sentinel nodes was the only positive nodes in this dissection. They were 0.8 and 0.6 cm large and the total of node dissected in theses regions were 7 and 10, respectively.

In the 24 inguinal regions with negative sentinel lymph node, no diagnostic changes occurred in any of them during lymph node dissection. Therefore, when we compared this method with the modified inguinal lymphadenectomy as the gold standard treatment, we found these values: 0% false negative, 66% sensitivity and 79.3% specificity. It is important to highlight that this false negative rate does not consider

the patient without detection of sentinel lymph node and positive lymphatic dissection.

Some more relevant data can be cited: a total of 297 lymph nodes were dissected, 157 on the right and 140 on the left, a mean number of 8.25 lymph nodes per region studied.

A study of the dissected lymph nodes confirmed the diagnosis of regional metastasis in all four clinically positive regions. Moreover, in all the patients who underwent classical radical dissection due to lymph node positivity, the positivity of the lymph nodes removed did not surpass the limits proposed by the modified dissection technique.

In four clinical positive regions, we found 10 positive nodes out of 35 dissected. These were mean 2.2 cm large and none was adhered to the adjacent tissues.

An evaluation of the distribution of these patients according to staging and histological grade revealed that six patients were pT1G1, 8 were pT2G1, 3 were pT2G2 and 1 was pT3G3. Metastasis was not detected in patients with T1 primary lesions.

The follow-up period ranged from 8 to 58 months, with a mean follow-up period of 28.3 months.

Two patients presented regional disease recurrence that was confirmed by the pathological exam and both patients presented positive surgical staging for metastasis in the inguinal regions. Both patients died two and four months after recurrence. These patients had presented with positive groins at initial diagnosis and were submitted to radical lymphadenectomy.

Another 81-year-old patient died three months after surgery but the cause was not directly related to the disease.

Table-1 demonstrates the above-described results.

COMMENTS

The literature demonstrates that after resection, 20% of clinically negative inguinal regions in patients with penile cancer have proved to be positive (7). This data underscores the importance of proposing some kind of treatment for patients in this condition, especially since prognosis is poor in patients with delayed diagnosis of lymph node metastasis (8).

Neglected regional adenopathy is not uncommon in underdeveloped countries after penile cancer treatment and in advanced cases, the inguinal mass can reach large sizes and little can be offered as a curative treatment (9).

Considering that groin is the first site of lymphatic dissemination of penile squamous cell carcinoma , inguinal involvement is one of the most important factors in survival prognosis and it is very common to lost follow-up of these patients in underdeveloped countries, we offer lymphadenectomy concomitant to penectomy in our institution (9).

On the other hand, lymph node dissection in the inguinal region can cause up to 80% morbidity (10,11). A better assessment can be obtained with a biopsy of a single or small group of sentinel lymph nodes as it allows for finer sections of the specimen and an immunohistochemical study whenever required (5).

In view of the fact that in 50% of positive cases, the sentinel lymph node was the only lymph node affected after ample dissection, it has been suggested that on the basis of parameters such as size of metastasis and histological grade of cell differentiation, only the sentinel lymph node should be removed even when it is positive (8,12).

Our study demonstrated that in two cases of sentinel lymph node positivity, the disease was restricted only to the sentinel lymph node in one case.

Another significant data was the false negative percentage, which in our study was 0% but in the literature is approximately 11 to 18% (4,5,13). We could have obtained similar results if the study sample was larger.

However, there were no cases of sentinel lymph node detection by the gamma camera without confirmation by the intraoperative portable probe, but in conformity occurred in 30% of the cases in the literature (4). This may be due to a technical change brought about by the lymphoscintigraphy, which was performed on the same morning as the surgery, indicating that the probe was used a few hours after the initial exam. Moreover, this technical change eliminated the need for a complementary exam with methylene blue (14,15).

Table 1 – *Cases studied and results obtained.*

Patient	Stage	Grade	Age	Right	Left	Right	Left	Node	Follow-up
1	PT2	II	60	excluded	no captation	excluded	(-)	N1	58
2	PT1	I	55	(-)	(-)	(-)	(-)	N0	55
3	PT2	I	50	(-)	(-)	(-)	(-)	N0	51
4	PT1	I	51	no captation	(-)	(-)	(-)	N0	47
5	PT1	I	63	(-)	(-)	(-)	(-)	N0	43
6	PT1	I	56	(-)	(-)	(-)	(-)	N0	33
7	PT2	I	44	(-)	(-)	(-)	(-)	N0	30
8	PT2	II	49	(-)	(-)	(-)	(-)	N0	29
9	PT2	I	81	(-)	excluded	(-)	excluded	N1	26
10	PT1	I	50	(-)	(-)	(-)	(-)	N0	24
11	PT2	I	45	(+)	no captation	(+)	(+)	N2	21
12	PT2	I	70	(-)	no captation	(-)	(-)	N0	19
13	PT2	I	52	(-)	(-)	(-)	(-)	N0	18
14	PT2	I	63	(-)	no captation	(-)	(-)	N0	15
15	PT2	II	65	(-)	excluded	(-)	excluded	N1	12
16	PT2	I	72	(-)	(-)	(-)	(-)	N0	10
17	PT3	II	66	excluded	(+)	excluded	(+)	N2	10
18	PT1	I	47	no captation	(-)	(-)	(-)	N0	8
			57.7						28.3 (SD 16.2)

SD = standard deviation.

Other noninvasive procedures have been used to detect inguinal metastases for penile cancer, including the use of lymphotropic nanoparticles enhanced magnetic resonance imaging (16).

Recently Horenblas et al. studied 50 patients with penile cancer and negative groins. These patients were submitted to SPEC-CT and lymphoscintigraphy utilizing the Daseler's five zones, that divide the groin region in four quadrants and one central zone on sapheno-femoral junction, they found that all sentinel nodes were in superior or central zones. In conclusion, they suggested that the dissection should be limited on and above the sapheno-femoral junction (17).

Some authors of Latin America have proposed endoscopic inguinal lymphadenectomy with decreased surgical morbidity, such as skin necrosis, wound infections and lymphedema. Although new endoscopic approaches to perform inguinal lymphadenectomy may decrease postoperative morbidity without compromising oncological control, sentinel lymph node biopsy may help improve patient selection for inguinal lymphadenectomy, preventing unnecessary procedures or indicating earlier surgery when lymph nodes are not yet palpable(18,19).

Although these novel noninvasive tests appear sensitive in preliminary reports, their ultimate value awaits further validation.

One of our cases of lymphatic metastasis with a clinically negative region occurred in a patient with an undetected sentinel lymph node. This resulted in a 66% test sensitivity that was comparable with the literature and reinforced the need for surgical exploration of the inguinal region without lymphoscintigraphic detection of the sentinel lymph node (4,5,20,21).

Although the sentinel biopsy decreases the morbidity in penile cancer treatment, there are limitations to a less aggressive approach and patients with undetected sentinel lymph node being considered a method limitation (22).

On the other hand, false-negative rate is encouraging and suggests that with experience and technical evolution lymphoscintigraphy could become a standard procedure requiring further optimization at high volume centers.

Taking into consideration that Catalona procedure fails to identify until 15 % of patients developing late metastasis, new methods are warranted in the future (3).

Considering the learning curve associated with lymphoscintigraphy and that penile cancer is a rare disease, the optimal lymphoscintigraphy technique is still in evolution, but it may be a very good option in the future.

CONCLUSION

Sentinel lymph node biopsy is a feasible method of assessing the presence of regional metastasis in patients with penile cancer and clinically negative inguinal regions. It does not appear to decrease oncological outcomes.

However, the optimal lymphoscintigraphy technique is still in evolution and requires further optimization at high volume centers.

CONFLICT OF INTEREST

None declared.

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Accepted after revision:
August 18, 2008

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EDITORIAL COMMENT

The best approach of patients T1-2N0M0 penile squamous cell carcinoma with intermediate and high risk of development of inguinal metastasis remains debatable.

A recent study suggests that Solsona and EUA stratification of risk for metastasis have low accuracy to select patients for inguinal dissection (1). To better access the risk of inguinal involvement, we now have a new instrument to guide the decisions. The nomogram of Ficarra et al. based on data of multicentric Italian group classify patients based in the most important prognostic factors as clinical lymph node stage and pathological data as tumor thickness, growth pattern, grade, lymphatic and vascular embolization, corpora

cavernosa and spongiosa infiltration (2). External validation for other populations is required for better acceptance of this instrument in clinical practice.

Fifteen to 25% of these patients have micrometastatic disease at time of local treatment. Radical inguinal lymphadenectomy can be curative for low volume disease but the majority of patients will receive a surgical procedure with morbidity higher than 50% (3). Wait and see policy has been advocate in the past but some recent data have showed that prophylactic dissection offer survival advantage compared to rescue lymphadenectomy after clinical recurrence (4).

Some authors suggest limited dissections. The reliability of this procedure had been questioned because some series reported up to 15% of late recurrence in other inguinal regions from initial dissection (5).

Anatomic sentinel lymph node as described by Cabanas has been abandoned because the high false negative results.

Dynamic visualization of lymphatic drainage by blue dye in melanoma patients resulted in a renaissance of the sentinel node concept in penile cancer in the mid-1990s. Some recent data of reference centers world wide showed that this technique has reduced morbidity but controversy remains as regards oncological results. This technique requires that specialists in urology, pathology, and nuclear medicine collaborate closely, and high standards are also essential in quality control (6-8).

The Netherlands data reported suggest that with constant improvements and standardization of the technique it proved possible to reduce the incidence of false-negative results with experience (6). In cohort A (1994 until 2001), 21 of 157 explored groins contained tumor-positive sentinel nodes, and five false-negative procedures were encountered, resulting in a false-negative rate of 19.2%. In cohort B (2001 until 2004), 20 of 105 explored groins contained tumor-positive sentinel nodes, and one procedure was false negative. The false-negative rate was 4.8%. The rate of complications dropped from 10.2% in cohort A to 5.7% in cohort B (1).

Data from United Kingdom showed that in 255 sentinel lymph node removed from 143 groins; all excised nodes had taken up the radioactive marker, and the blue dye was evident in 87%. Eighteen of 75 (24%) patients and 21 of 143 groins (15%) had a positive sentinel. Six of 143 (4%) groins developed minor complications. Only one false-negative result was reported at a median (range) follow-up of 11 (2-24) months (7).

On the other hand, in the MD Anderson (8) experience 6 of 32 groins that showed drainage on preoperative lymphoscintigraphy had inguinal node metastasis, as did 1 of 10 that was drainage negative. The sensitivity of preoperative lymphoscintigraphy drainage for cancer detection was 86%. Using dynamic sentinel node biopsy with blue dye plus radiotracer 5 sentinel lymph nodes were positive for cancer, although 2 false-negative results were obtained. Thus, the sensitivity of dynamic sentinel node biopsy per groin for cancer detection was 71%. Authors believe that preoperative lymphoscintigraphy and dynamic sentinel node biopsy as currently performed remain insufficient for detecting occult inguinal disease. They suggest that superficial lymph node dissection remains the gold standard for detecting inguinal microscopic metastasis in these patients (8).

The authors of this interesting manuscript consider that the false negative was 0% but 2 patients (11%) died of late inguinal recurrence in some area considered to have no metastasis. Due to the design of this study, we do not know which will be the outcome if patients when the sentinel was not detected would be received radical dissection.

Conservative management of inguinal regions have some particular problems in Brazilian population. Due to the low socio economic level of these patients, the follow up is not executed as recommended. We believe that the non detected cases at initial evaluation can result in loose the window of cure.

Based in this discussion of the literature and considering that there are no ideal method to locate inguinal micrometastasis I and my colleagues of ABC Medical School proposed a radical dissection applying the principals of minimally invasive surgery. This procedure was designed to achieve reduction in morbidity without jeopardize the oncological control. Preliminary data obtained in 22 dissected groins in 16 patients followed by 36 months showed reduced morbidity and no recurrence compared to open

conventional surgery (9). Other multicenter Latin America study has also showed the reduced morbidity of endoscopic approach (10).

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EDITORIAL COMMENT

The manuscript reports on the value of sentinel lymph node biopsy using lymphoscintigraphy in patients with penile cancer and at least one negative inguinal region. Lymphoscintigraphy with peritumoral intradermal injection of technetium 99m was used to identify the sentinel lymph node. A comparative study using modified inguinal dissection was performed in these regions regardless of the biopsy results. I believe that it is an experimental method with 66% sensitivity, and 79.3 % specificity when compared with the modified inguinal lymphadenectomy in this manuscript. I agree with the authors´ conclusion that the optimal lymphoscintigraphy technique is still in evolution and requires further optimization at high volume centers. The manuscript is well written and the authors are to be congratulated for their interesting work.

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EDITORIAL COMMENT

Sentinel lymph node biopsy (SLNB) is a novel diagnostic modality for the assessment of inguinal lymph nodes in penile cancer patients without palpable inguinal adenopathy. It offers the potential of reduced morbidity without compromising cancer detection accuracy as compared to modified inguinal lymph node dissection. However, while it is true some groups such as the Netherlands Cancer Institute (references 7 and 11) have shown promising results with SLNB, its cancer detection accuracy has been shown to be operator dependent and associated with a steep learning curve. This is why the reported false negative rate for cancer detection has ranged from 0 to 22% (depending on the reported series). Before establishing SLNB as the "gold standard" for the diagnostic evaluation of the inguinal region of penile cancer patients without palpable adenopathy, its results must be more consistently reported across multiple centers and its reduced morbidity versus modified inguinal lymph node dissection must be confirmed. Similarly, emerging diagnostic modalities including video endoscopic inguinal lymph node dissection and nanoparticle MRI may prove superior to SNLB in terms of cancer detection and surgical morbidity. As such, recent advances in radiologic imaging and minimally invasive surgical approaches offer the potential to redefine the diagnostic and treatment standards for the management of penile cancer patients.

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REPLY BY THE AUTHORS

In the first editorial comment, the authors state in the 10th paragraph that 2 patients (11%) died of late inguinal recurrence in some area considered to have no metastasis. However, according to paragraph 13 in results section of article, both patients presented positive groins at initial diagnosis and were submitted to radical lymphadenectomy. So, these patients were not considered as method fail.

We recommend radical lymphadenectomy when the sentinel lymph node was not detected, due to a possible erratic drainage caused by blockage due to a grossly involved impalpable metastatic lymph node. There are limitations to a less aggressive approach and patients with undetected sentinel lymph node are considered a method limitation, which explains in part 0% false negative and 66% sensitivity in the article. The optimal lymphoscintigraphy technique is still in evolution and requires further optimization associated with advances in radiologic imaging and minimally invasive surgical approaches.

Emerging diagnostic modalities including video endoscopic inguinal lymph node dissection, nanoparticle MRI and sentinel lymph node biopsy may prove superior or either complementary among others in terms of cancer detection and surgical morbidity.

The Authors

Surgical Technique

International Braz J Urol Vol. 34 (6): 734-738, November - December, 2008

Pure Robotic Retrocaval Ureter Repair

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ABSTRACT

Purpose: To demonstrate the feasibility of pure robotic retrocaval ureter repair.
Materials and Methods: A 33 year old female presented with right loin pain and obstruction on intravenous urography with the classical "fish-hook" appearance. She was counseled on the various methods of repair and elected to have a robot assisted repair. The following steps are performed during a pure robotic retrocaval ureter repair. The patient is placed in a modified flank position, pneumoperitoneum created and ports inserted. The colon is mobilized to expose the retroperitoneal structures: inferior vena cava, right gonadal vein, right ureter, and duodenum. The renal pelvis and ureter are mobilized and the renal pelvis transected. The ureter is transposed anterior to the inferior vena cava and a pyelopyelostomy is performed over a JJ stent.
Results: This patient was discharged on postoperative day 3. The catheter and drain tube were removed on day 1. Her JJ stent was removed at 6 weeks postoperatively. The postoperative intravenous urography at 3 months confirmed normal drainage of contrast medium.
Conclusion: Pure robotic retrocaval ureter is a feasible procedure; however, there does not appear to be any great advantage over pure laparoscopy, apart from the ergonomic ease for the surgeon as well the simpler intracorporeal suturing.

Key words: *ureter; vena cava; abnormalities; laparoscopy; robotics*
Int Braz J Urol. 2008; 34: 734-8

INTRODUCTION

Retrocaval ureter is an unusual urological problem that may require operative repair (Figure-1). The first case of retrocaval ureter repair was published in 1949 by Anderson and Hynes (1). The classical approach is an open technique of transposing the ureter anteriorly to the inferior vena cava followed by ureteroureterostomy. Laparoscopic retrocaval ureter repairs have also been performed but can be technically challenging. This is the first case of a pure robotic repair, to our knowledge, performed in an adult. We present our robotic technique of pure robotic retrocaval ureter repair.

SURGICAL TECHNIQUE

1. Patient position - The patient is positioned in a modified flank position over the kidney break at a 45 degree angle. The patient is then adequately secured with supports and strapping, and all pressure areas are protected.

2. Port position - A Veres needle is used to create a pneumoperitoneum, then a 10 mm port is inserted for the camera at the level of the umbilicus just lateral to the rectus abdominis muscle. Two 8 mm ports are inserted for the robotic arms, one under the costal margin in the midclavicular line and the other at two thirds of the way along McBurney's line (anterior

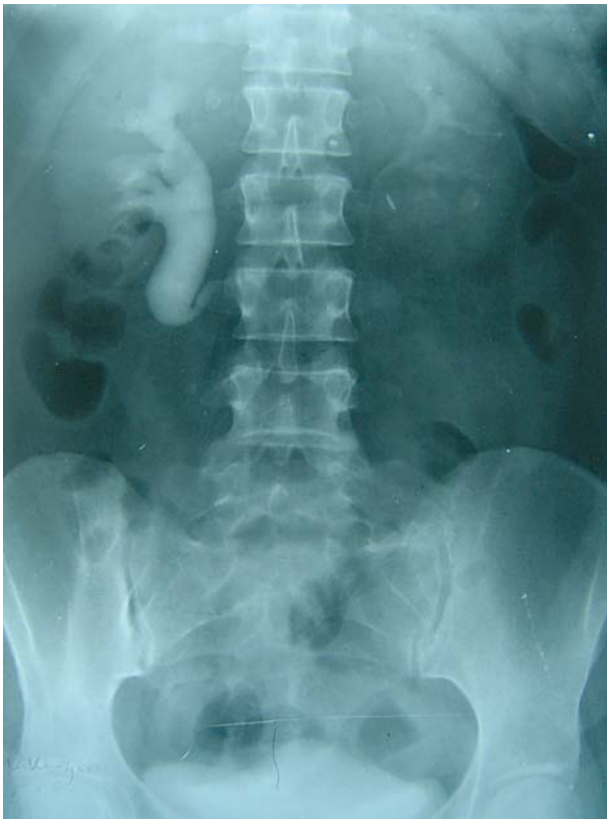

Figure 1 *– Pre-operative IVU.*

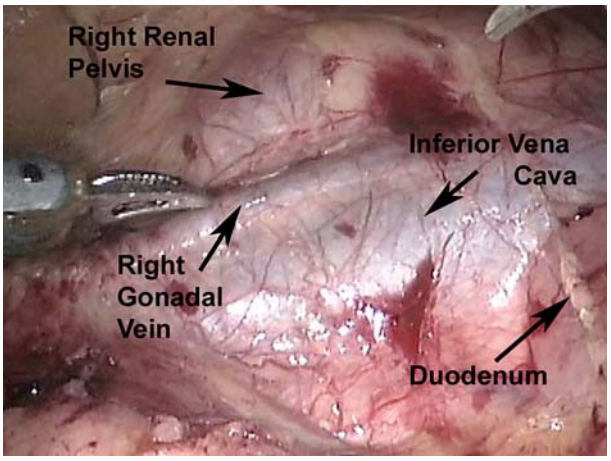

Figure 2 *– Exposure.*

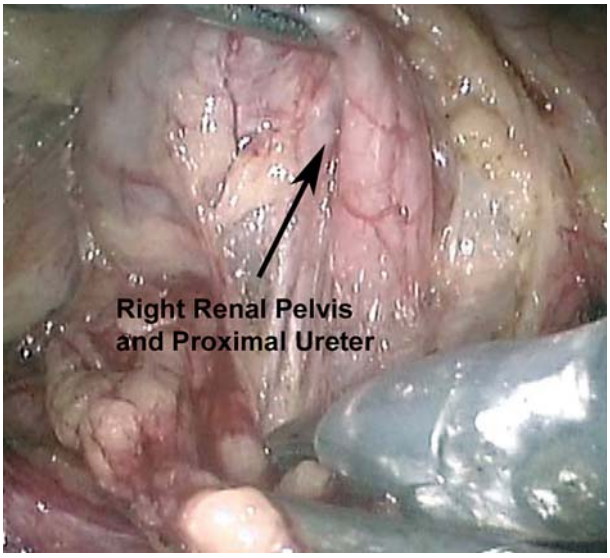

Figure 3 *– Mobilization of renal pelvis and ureter.*

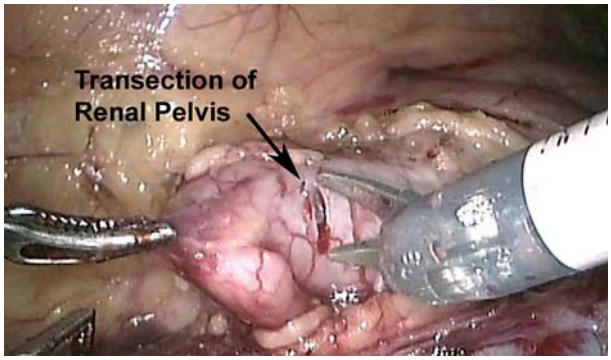

Figure 4 *– Transection of renal pelvis.*

superior iliac spine and umbilicus). A further 5 mm port is inserted 3 cm below the camera port for the assistant to perform retraction and suction. The robot is then docked. The whole process of pneumoperitoneum, port insertion and docking takes 15 minutes.

3. Colon mobilization - The hepatic flexure and right colon are mobilized medially to provide exposure to the right retroperitoneal structures.

4. Exposure of retroperitoneal structures: (Figure-2). The right renal pelvis, inferior vena cava, right gonadal vein, right ureter and duodenum are all identified.

5. Mobilization of renal pelvis and ureter: (Figure-3). The right renal pelvis is dissected free from its surrounding fascial layers. The proximal right ureter is dissected free where it can be seen to disappear superiorly under the inferior vena cava.

6. Transection of ureteropelvic junction: (Figure-4). The renal pelvis is transected and the

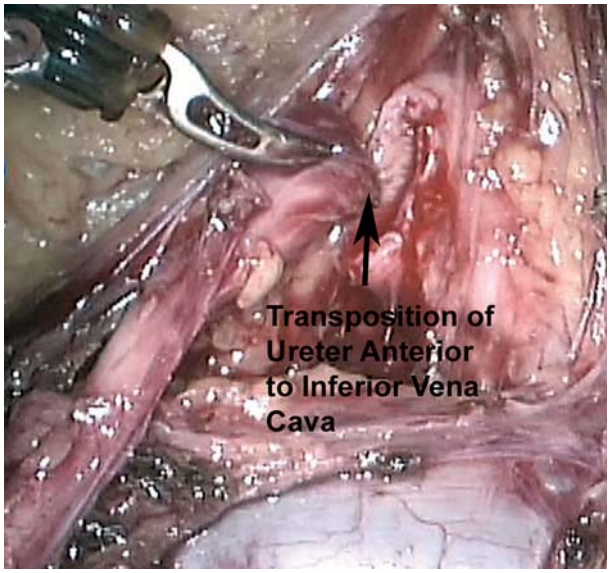

Figure 5 – *Transposition of ureter.*

ureteropelvic junction along with the retrocaval segment are transposed anterior to the inferior vena cava (Figure-5) in preparation for a pyelopyelostomy. This may not be possible for lower segment retrocaval ureters in which case ureteroureterostomy must be performed.

7. Pyelopyelostomy: (Figure-6). Performing a pyelopyelostomy is easier than a ureteroureterostomy and one is less likely to produce stricture formation due to the larger caliber structures as well as the better blood supply as one goes more superiorly. This is performed with 40 polygalactin suture material in an interrupted fashion.

8. Antegrade JJ stent insertion: (Figure-7). Prior to closing the anastomosis, a 6F JJ stent is inserted in an antegrade fashion. The stent with the wire is introduced via the 5 mm port. It is grasped using the robotic needle holder, introduced into the ureter and passed down to the bladder.

9. Drain tube insertion: The robot is undocked and a drain tube is inserted via the 5-mm port. The 10 mm port is closed in standard fashion and an indwelling catheter is left in situ.

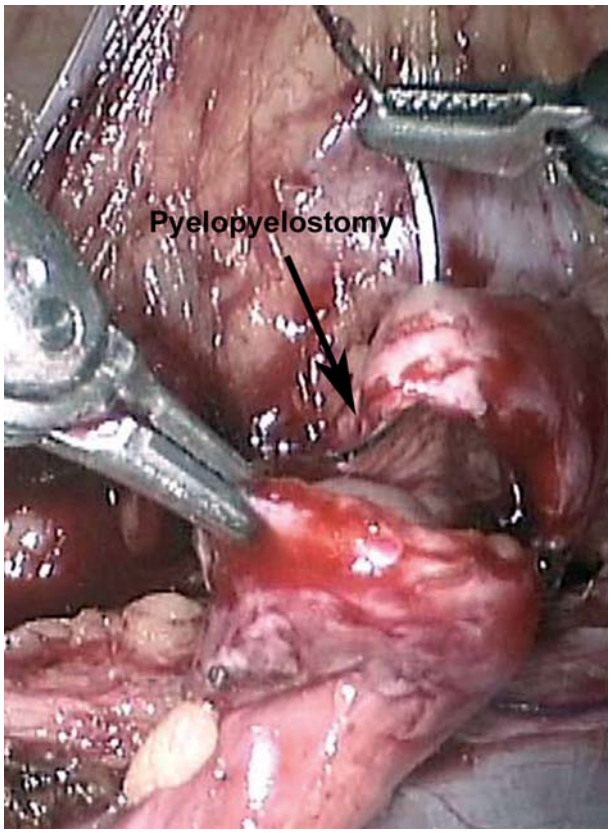

Figure 6 – *Pyelopyelostomy.*

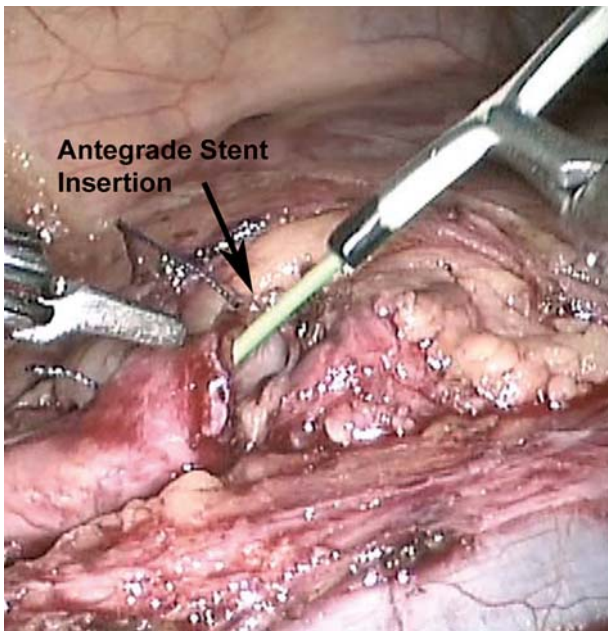

Figure 7 – *Antegrade JJ stent insertion.*

RESULTS

This 33 year old female patient was discharged on postoperative day 3. The catheter and drain tube were removed on day 1. The JJ stent was removed at 6 weeks post operatively. The post operative IVU at 3 months confirmed normal drainage of contrast (Figure-8).

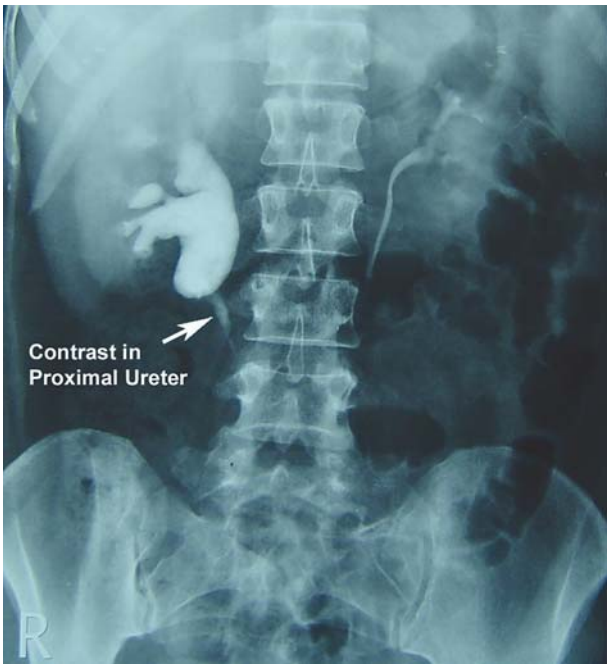

Figure 8 – *Postoperative IVU.*

COMMENTS

Robotic technology has become incorporated into certain areas of urology as in robotic prostatectomy and has become well accepted. Reconstructive urology represents a challenge for the robotic urologist to offer this technology safely, with efficacy over proven techniques and without increased morbidity.

Our case demonstrates the feasibility of a procedure using the robot but does not necessarily justify its use over other modalities. Though the fundamental surgical principles of a tension free, well vascularized anastamosis remain the same, patients may now receive the benefits of a minimally invasive approach, namely: smaller incision; better cosmetic effect, decreased pain; shorter hospital stay and a quicker return to normal activities. This holds true for both a pure laparoscopic or pure robotic approach.

Pure laparoscopic repair of the retrocaval ureter has been performed both transperitoneally and retroperitoneally (2). We have previously published our results with retroperitoneal ureterolysis and retrocaval ureter repair (3). Pure laparoscopic repair remains a technically challenging procedure, but in experts hands the results are excellent.

The robotic approach to retrocaval ureter was first published for a pediatric patient by Gundeti et al. in 2006 (4). Pyelopyelostomy with preservation of the retrocaval segment was first performed for a retrocaval ureter by Simfiroosh et al. in 2006 in a pure laparoscopic procedure (5). This preservation of the retrocaval segment does not appear to hinder drainage and it makes the anastamosis far easier to perform and may lead to a lower stricture rate.

The main advantage of the robotic technology is the ease of dissection and intracorporeal suturing. Expert laparoscopic surgeons may argue that there is no need for the robot in such a procedure in the same way that laparoscopic pyeloplasty can be done without the robot. This of course is true, however the fact remains that new technologies emerge and it seems that robotic technology is here to stay. The downside to the robotic approach is of course the cost.

Since acquiring the da-Vinci-S robot in 2006 we have performed many reconstructive procedures such as megaureter repair and pyeloplasty with robotic assistance. This is the first retrocaval ureter repair that we have performed using the robot.

CONCLUSION

We demonstrated in this case that pure robotic retrocaval ureter repair is feasible. Apart from the ergonomic and technical benefits that the robotic approach gives the surgeon, there does not appear to be any other advantage over laparoscopy.

CONFLICT OF INTEREST

None declared.

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Accepted after revision:
August 28, 2008

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Pediatric Urology

International Braz J Urol Vol. 34 (6): 739-748, November - December, 2008

Laparoscopic Renal Surgery in Infants and Children: Is it a Feasible and Safe Procedure for all Pediatric Age Groups?

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ABSTRACT

Purpose: Although laparoscopy is considered the mainstay for most renal procedures in adults, its role in the pediatric population is still controversial, especially for smaller children. We reviewed our experience in pediatric renal laparoscopic surgery in three pediatric age groups in an attempt to identify if age has an impact on feasibility and surgical outcomes.
Materials and Methods: From November 1995 to May 2006, 144 pediatric laparoscopic renal procedures were performed at our institution. The charts of these patients were reviewed for demographic data, urologic pathology and surgical procedure, as well as perioperative complications and post-operative outcomes. The findings were stratified into 3 groups, according to patient age (A: < 1 year, B: 1 to 5 years and C: 6-18 years).
Results: Median age of the patients was 4.2 years (42 days - 18 years). We performed 54 nephrectomies, 33 nephroureterectomies, 19 upper pole nephrectomies, 11 radical nephrectomies, 22 pyeloplasties and 4 miscellaneous procedures. The 3 age groups were comparable in terms of the procedures performed. Conversion rates were 0%, 1.4% and 1.9% for groups A, B and C, respectively ($p = 0.72$). Incidence of perioperative complications was 5%, 8.2% and 7.8% for age groups A to C, respectively ($p = 0.88$).
Conclusions: Most renal procedures can be performed safely by laparoscopy in the pediatric population, with excellent aesthetic and functional outcomes. The morbidity related to the procedure was minimal irrespective of the age group.

Key words: *pediatrics; laparoscopy; renal surgery; complications; results*
Int Braz J Urol. 2008; 34: 739-48

INTRODUCTION

Although laparoscopy is considered the mainstay for most renal procedures in adults, its role in the pediatric population is still controversial, especially for smaller children (1-3).

In pediatrics, traditional open renal procedures have enjoyed high success rates. Moreover, infants and smaller children tend to experience less postoperative morbidity than adults (4,5). To date, there are very few reported series comparing open and laparoscopic renal procedures (6-9).

Despite these drawbacks, there is an increasing interest in the laparoscopic procedures by pediatric urologists, due to miniaturization of the laparoscopic equipment and better post-operative course, as well as by the parents of patients, due to obvious cosmetic advantages. Nevertheless, there are very few works addressing the possible limitations deriving from the small corporeal size in the application of the method

(10-12). The primary objective of this study was to review indications, feasibility and safety in 3 pediatric age groups, in order to determine if younger (hence smaller) children are at an increased risk for conversion or complications when undergoing a laparoscopic renal procedure. As a secondary objective, we have also reviewed the outcomes of these procedures during follow-up.

MATERIALS AND METHODS

From November/1995 to May/2006, a total of 141 children underwent 144 laparoscopic procedures involving the kidney; 3 of these patients had asynchronous bilateral procedures. The age of the patients ranged from 42 days to 18 years (median of 4.2 years). For analysis of feasibility and safety, patients were subdivided into 3 groups: A: (1-11 months), B: (1-5 years) and C: (6-18 years). Table-1 shows the demographics of these 3 age groups.

The most common indications for each kind of laparoscopic procedure were as follows. Simple nephrectomy: non-functioning kidneys due to ureteropelvic junction (UPJ) obstruction, stenosis of the renal artery or multicystic kidney; three cases had a nephrological indication for nephrectomy, for reduction of proteinuria in cases of nephrotic syndrome. Nephroureterectomy: functional exclusion due to vesicoureteric reflux (VUR), ureterocele, ectopic ureter or primary obstructive megaureter. Upper pole nephrectomy (UPN): functional exclusion of the upper pole in ureteropelvic duplication. Radical nephrectomy: renal tumors (1 renal cell carcinoma, 1 cystic nephroma, 1 mass that was shown later to be a xantogranulomatous pyelonephritis, 8 cases of post-chemotherapy Wilms' tumors) (13-15). Pyeloplasty: UPJ obstruction with functioning kidney. Two of these patients presented with associated pelvic and calyceal stones and underwent a laparoscopic pyelolithotomy during the same procedure.

The procedures described as miscellaneous include 2 resection of large compressive renal cysts and 2 bilateral nephrectomies in which the kidneys and ureters were mobilized downwards, exposed through a Pfannenstiel incision, detubularized and sutured to the bladder as a means of augmentation.

The laparoscopic renal procedures included in this study and their distribution in each age group is shown in Table-2.

Surgical Technique

The surgeries were carried out under general anesthesia, and continuous monitoring, including capnography. The patients received bladder and gastric catheterization, were kept warm by a thermal blanket and hydrated with warmed crystalloid solution..

The transperitoneal access was employed in the majority of cases (n = 140). The initial access was made with a Veress needle, except in the few cases with previous abdominal surgery or marked obesity, in which a Hasson (open) technique was used. In 4 cases,

***Table 1** – Demographic data and side of the pathology in the population and in the 3 age groups.*

Age Group	**N of Cases**	**Mean Age** (range)	**M**	**F**	**R**	**L**	**Bilateral**
A (< 12 months)	20	6.2 months (42 days to 11 mo.)	9	11	7	13	0
B (1 to 5 years)	73	3.1 years (1y1mo. to 5y11 mo.)	47	26	34	38	1
C (6 to 18 years)	51	9.6 years (6 years. to 18 years)	23	28	20	27	4
Total	144	5.0 years (42 days to 18 years)	79	65	61	78	5

M = male; F = female; R = right; L = left; p > 0.05 for gender and side distribution among the 3 age groups.

Table 2 – *Number of procedures performed in each age group.*

Age Group	N of Cases	N	NU	UPN	RN	Pp	Miscellaneous
A (< 12 months)	20	6	7	4	0	3	0
B (1 to 5 years)	73	31	15	8	7	10	2
C (6 to 18 years)	51	18	11	7	4	9	2
Total	144	55	33	19	11	22	4

N = nephrectomy; NU = nephroureterectomy; UPN = upper pole nephrectomy; RN = radical nephrectomy; Pp = pyeloplasty; Misc = miscellaneous procedures. p = 0.69 for differences in the frequency of the procedures among the 3 age groups.

a lateral retroperitoneoscopic access was employed (2 pyeloplasties and 2 nephrectomies).

The pressure of CO_2 insufflation ranged from 8 to 14 mmHg, according to the patient weight.

Details of the surgical technique have been previously described, but some technical points should be stressed (9-11,15-17). In the UPN, after exposing the hilum, the diseased ureter is divided distally, almost always at the level of the iliac vessels, preserving the normal ureter. The distal stump is aspirated in cases of ureteroceles. It is then transposed cranially underneath the hilum and used as a handle to identify and manipulate the diseased upper pole. This maneuver facilitates the visualization of the upper pole vessels and the transection of the parenchyma between the poles. Pyeloplasties were performed after a retrocolic exposure of the UPJ. A transabdominal hitch stitch was used to stabilize the pelvis. In 19 cases, the Anderson-Hynes dismembered technique was performed. A technically simpler alternative was employed in 3 cases, in which there was a high insertion of the ureter in the pelvis, allowing a latero-lateral ureteropelvic anastomosis without section of the UPJ.

In all pyeloplasties except one, a double J catheter was inserted antegrade before completion of the anastomosis, which consisted of a running suture with 5 or 6-0 Vicryl thread. In the cases that presented with associated calyceal and pelvic stones, fluoroscopy, stone graspers and a flexible nephroscope were used for lithotripsy.

Patients remained hospitalized until stabilization of pain and gastrointestinal symptoms.

Patients undergoing pyeloplasty had an indwelling bladder catheter for 2-3 days. The double J catheter was removed by endoscopy after 4-6 weeks. All patients were medicated with an analgesic and antibiotics in the postoperative period.

Study Design

The medical records were reviewed; perioperative and follow-up outcomes, as well as occasional late complications related to the technique were recorded.

The statistical analysis was performed using "chi-square" test or the likelihood ratio test for differences between proportions, and the Student-t-test for differences between means, $p < 0.05$ being considered statistically significant.

RESULTS

Group A (1 to 11 months of age; n = 20). All procedures were completed successfully. There was no need for conversion to open surgery in any cases, and there were no major complications.

Intraoperative bleeding was minimum in all cases. Only one (5%) intraoperative incident was observed, in an 11 month-old baby boy with left renal exclusion due to VUR and ureteral quadruplication, who underwent a laparoscopic nephroureterectomy. This patient had an atretic left vas deferens, which adhered to the dilated distal ureter, and was sectioned during the procedure.

All patients began feeding in the immediate postoperative period, and there were no postoperative incidents.

The late follow-up of these patients showed no important incidents related to the procedure. During the follow-up, all patients who underwent upper pole polar nephrectomies presented good function in the remaining inferior unit in the renal scintigraphy and all three patients who underwent pyeloplasties presented clinical and radiological signs of success.

Group B (1 to 5 years of age; n = 73). Seventy-two cases (98.6%) could be completed laparoscopically, while only one case needed conversion to open surgery: in the 4th case of our series, a 2 year-old girl undergoing a left nephrectomy due to non-functioning hydronephrosis was found intraoperatively to have a horseshoe kidney with a fleshy isthmus. As this was still at the beginning of our laparoscopic experience, and fully adequate equipment was not yet available, we decided for the division of the isthmus and removal of the specimen through a small laparotomy.

There were no major complications, and six cases (8.1%) presented with minor complications, including 4 hemorrhagic complications and 2 prolonged postoperative ileum.

In 2 radical nephrectomies for Wilms´ tumors, in one nephrectomy and in 1 UPN there was bleeding during or after the surgery that required blood transfusion (10-15 mL/kg). In the remainder of cases, bleeding was negligible.

Except for 2 cases (2.7%) that presented an adynamic ileus until the 4th post-operative day, the patients had normal oral intake within the first two postoperative days. A summary of all postoperative incidents is depicted in Table-3.

In the late follow-up, 3 events were noted, all in patients with duplication anomalies. A young boy who had undergone an UPN at the age of 13 months persisted with urinary tract infections and VUR to the lower pole and needed an open ureteral reimplantation. A girl who underwent UPN at the age of 5 years developed a distal ureteral empyema and needed a laparoscopic distal ureterectomy. A young boy who underwent UPN at the age of 16 months developed an asymptomatic functional loss of the ipsilateral inferior renal unit, probably due to accidental injury of the main renal artery during surgery.

Regarding the late follow-up of pyeloplasties, all patients showed clinical and radiological evidence of success. The 2 patients who underwent a laparoscopic pyelolithotomy became stone free.

The seven radical nephrectomies were performed in patients with Wilms´ tumor, after good response to neoadjuvant chemotherapy (12). No tumor rupture occurred in any of the cases, and neither local nor systemic recurrences were observed, after a mean follow-up of 33 months.

Group C (> 5 years of age; n = 51). Fifty (98%) procedures were completed laparoscopically. A single case needed a tactical conversion to open surgery (2%). A 9 year-old girl undergoing a radical nephrectomy for a renal cell carcinoma had an extensive adherence between the mass and the diaphragm, resulting in diaphragm laceration during dissection. A subcostal incision was made to remove the specimen and facilitate the closure of the diaphragm. The postoperative course of this patient was uneventful.

Table 3 – *Frequency of perioperative complications in each age group.*

Age Group	Conversion to Open Surgery	Hemorrhagic Complications	Urinary Fistula	Prolonged Postoperative Ileus	Other Perioperative Complications	Overall Perioperative Complication
A (< 12 months)	0	0	0	0	1 (5%)	1 (5%)
B (1 to 5 years)	1(1.4%)	4 (5.5%)	0	2 (2.7%)	0	6 (8.2%)
C (6 to 18 years)	1(2%)	1 (2%)	1 (2%)	2 (3.8%)	0	4 (7.8%)
Total	2 (1.4%)	5 (3.5%)	1 (0.7%)	4 (2.8%)	1 (0.7%)	11 (7.6%)

p = 0.72 for differences in conversion rates among the 3 age groups. p = 0.88 for differences in perioperative complications among the 3 groups.

There were no major complications. Minor complications occurred in 4 (7.8%) cases: one significant intraoperative bleeding, two cases of prolonged postoperative ileum and one case of urinary fistula in a patient who underwent a pyeloplasty, in whom the intraoperative antegrade insertion of a double J catheter was not possible. Despite being kept with the bladder catheter, the patient developed an anastomotic urinary leakage, and required a retrograde insertion of a double J catheter in the 8th post-operative day (POD). After that, the follow-up was excellent with discharge by the 10th POD.

All patients had normal oral intake within the first two postoperative days, except for two cases that presented with prolonged ileus, which subsided spontaneously in the 5th POD. Regarding the late follow-up of these patients, only 2 events were observed. A boy who had undergone a nephroureterectomy when he was 11 years-old persisted with an obstructive ureterocele and needed an endoscopic puncture. A girl who underwent a UPN at the age of 13 years developed a distal ureteral empyema and needed a laparoscopic distal ureterectomy.

The late results of all pyeloplasties in this group of patients were favorable as well, without other complications.

In the four radical nephrectomies of this group, the pathological studies disclosed one xantogranulomatous pyelonephritis, one cystic nephroma, one clear cell carcinoma and one Wilms´ tumor. The patients with neoplasms had no signs of local or systemic tumor recurrence after an average follow-up of 33 months.

Comparative Analysis

Although the first group is smaller, the demographics of the groups are comparable (Table-1). The procedures are evenly distributed in all groups, p = 0.69 (Table-2).

Table-4 illustrates the main operative and postoperative data in the 3 age groups.

There were no differences among the groups regarding conversion (p = 0.72) or perioperative complications (p = 0.88) (Table-3). Also, when comparing the incidence of complications between the simpler (nephrectomies and nephroureterectomies) and more complex (Radical Nephrectomies, Upper Pole Nephrectomies and Pyeloplasties) procedures, no difference was found (p = 0.66, 0.39, 0.46 and 0.47 for Groups A, B, C and the whole population).

Table 4 – *Operative and postoperative data for simpler and more complex procedures in each age group.*

	A (I - II months)	**B** (1 - 5 years)	**C** (> 5 years)	**p Value**
Simpler Procedures (N, NU)				
Mean operative time (range)	139 min. (60-210)	135 min. (40-225)	128 min. (70-240)	n.s.
Perioperative complications	7.7%	4.3%	10.7%	0.642
Mean time to discharge (range)	2.3 days (1-6)	2.1 days (1-5)	1.9 days (1-5)	n.s.
More Complex Procedures (RN, UPN, Pp)				
Mean operative time (range)	153 min (120-180)	197 min (150-270)	168 min (110-270)	n.s.
Perioperative complications	0	16%	5%	0.366
Mean time to discharge (range)	3.75 days (3-8)	3.2 days (2-5)	4.2 days (2-10)	n.s.

N = nephrectomy; NU = nephroureterectomy; UPN = upper pole nephrectomy; RN = radical nephrectomy; Pp = pyeloplasty; n.s. = non-significant difference between any 2 Groups.

COMMENTS

Adequate training and availability of new technologies have allowed the progressive increase in the indications of laparoscopic procedures in pediatric urology. Reconstructive and ablative renal procedures have been reported with increasing frequency, with safety and success (9-12,17). The presence of malignant pathology was one of the few limitations yet to be transposed in pediatric renal laparoscopy. We have recently described the successful treatment of Wilms´ tumor in children by laparoscopic nephrectomy (14,15). Moreover, we included in this sampling the laparoscopic treatment of a patient with clear cell carcinoma and other with cystic nephroma, with therapeutic success after a follow-up longer than 19 months.

The frequently described advantages of laparoscopic surgery are not always observed in simple nephrectomies, since incisions of open surgery can be small and recovery of children, particularly the younger ones, tends to be fast. Nevertheless, it must be stressed that very small incisions do not always allow a safe exposure of the renal pedicle and neighboring structures, favoring occasional accidents (4).

Despite being a parameter difficult to evaluate objectively, the parental satisfaction is prone to be more significant in laparoscopic procedures, due to the excellent cosmetic results as well as the smaller number of necessary dressing exchanges. Regarding nephroureterectomies, the laparoscopic choice presents clear advantages, considering that the open access may imply an additional lower incision to remove the distal ureter.

The polar nephrectomy is one of the new procedures in which laparoscopy seems more appealing, since it allows excellent visualization of the vascular pedicles and the renal units, with minimum mobilization of the lower moiety and excellent results concerning the preservation of this unit (18).

Pyeloplasty is still considered a technically demanding procedure, but has been reported with increasing frequency, with results that match open surgery, and clearly surpass those of endopyelotomies, whose late results are poor (19,20). The insertion of double J catheter was preferably antegrade during the laparoscopic pyeloplasty, facilitating the section of the UPJ and the anastomosis, as well as saving time by skipping cystoscopy and patient repositioning. Insertion of a double J catheter was not possible in only one patient. Postoperative results were excellent in all cases.

Despite an increased technical difficulty in smaller children, all procedures were feasible, independent of age and body size. In fact, we have observed that the access to the renal vessels or to the UPJ was very fast in many of the patients in Group A, due to the scarcity of peri-renal fat in young infants, which facilitated the surgery significantly. In smaller patients, we have routinely chosen to perform pyeloplasties transperitoneally, due to the larger working space, that allows a comfortable pieloureteral anastomosis. This has been the choice of the majority of authors (10,11,17).

The operative times shown at this study must be analyzed with some restrictions, due to the heterogeneity of the surgeries, the effect of the learning curve and the participation of different residents in training. Despite these remarks, we can observe that most procedures could be accomplished at reasonable operative times, even in the smaller children.

Moreover, the hospitalization times shown here are slightly longer than those usually reported for laparoscopic procedures elsewhere. This can be explained by the some particularities of our Institution, where many patients come from other regions of the country and may require longer hospitalization due to difficult return for early follow-up.

Regarding the safety of the laparoscopic access in the 3 age groups during this study, no major complications or accidents occurred in any of the cases. There were only two tactical conversions to open surgery, none in emergency scenario. Incidents during the procedures and on the immediate postoperative period (bleeding and adynamic ileus) were rare in all age groups. Of note, our rate of complication was small and not clearly dependent on the complexity of the procedure. This may have been observed at this series because many patients undergoing nephrectomy had associated conditions, such as inflammation, nephrological pathology or previous adhesions, which rendered an otherwise simple operation into a more difficult one.

In the late follow-up, there were 5 complications, but in 4 cases there was no relationship to the

laparoscopic access itself, but rather to lower urinary tract pathology (distal stump empyema, VUR and persistence of an obstructive ureterocele). The other event (loss of the lower pole after UPN) is also well described in open procedures (5).

CONCLUSIONS

Most ablative and reconstructive renal procedures can be performed safely by laparoscopy in the pediatric age group, with excellent functional and aesthetic outcomes. The feasibility was excellent and the morbidity of the procedures was minimal irrespective of the age of the patients.

Ideally, a prospective randomized study is needed to assess in which age groups, if in any, laparoscopy is superior to the open procedure. However, our study suggests that laparoscopy is a feasible and safe alternative that can be offered in the cases when renal surgery is required.

CONFLICT OF INTEREST

None declared.

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Accepted after revision:
August 25, 2008

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EDITORIAL COMMENT

Minimally invasive surgery is evolving fast in the field of pediatric urology. The advantages for some indications like ablative procedures as nephroureterectomy (including for donation) and partial nephrectomy for duplicated systems are real and here to stay (1,2). As in the present study, several authors showed that both transperitoneal laparoscopic or retroperitoneoscopic procedures were performed safely in all pediatric age groups with minimal morbidity and excellent short-term results (1-3).

On the other hand, reconstructive procedures are difficult to perform and dependent on special skills. With increasing improvement of the suture techniques, laparoscopic pyeloplasty represents, in experienced hands, an alternative method with success rates comparable to the open technique in success rates (4,5).

Comparative studies indicate that laparoscopic surgery achieves minimal morbidity such as pain and a quick return to normal activities. The hospital stay is significantly reduced, although the operative times are long compared with open pyeloplasty (5). Additionally, a recent report of morbidity and inflammatory response comparing open and laparoscopic pyeloplasty in the pediatric population show that shorter hospital stay and decreased cytokine response following laparoscopic indicates potential benefits over traditional invasive procedures (6).

However, at present time, experience with reconstructive procedures in children remains limited. Concerning pediatric laparoscopic pyeloplasty it is not clear if children younger than 1 year, where the open incision can be small, will benefit from this procedure. In this present series only 3 children in this age group underwent pyeloplasty but promising results seem to be reported.

Some alternatives reported to simplify the repair, which reduce operative time and achieve better results include laparoscopic dissection with extracorporeal reconstruction and robotic assisted surgery (7,8).

Sukumar et al. report 13 children who underwent laparoscopic assisted dismembered pyeloplasty. Using 5 mm camera and 3 mm working ports, the ureteropelvic junction (UPJ) was mobilized by a transperitoneal laparoscopic technique. The UPJ was withdrawn through a tiny flank incision and a standard dismembered pyeloplasty was performed over a double J stent. Mean operative duration was 104.2 min (range 80-150 min. Incision was smaller than 2

cm and the average postoperative hospital stay was 3.2 days. That authors believe that this technique has results comparable to that of open pyeloplasty and hence, maybe considered a good option for surgeons making the transition to pure laparoscopic pyeloplasty (7).

Robotic pediatric urologic procedures such as pyeloplasty, ureteral reimplantation, partial or total nephrectomy with or without ureteral stump removal are now done on a regular basis at select centers offering robotic expertise. The minimally invasive surgery using robotic da Vinci surgical system provides delicate manipulation, coalesced with three-dimensional visualization and a superior magnification. This has been considered the bridge between laparoscopy and open surgery. Some authors believe that in small children robotic surgery achieve a better quality of ureteral anastomosis than regular laparoscopic procedure (8).

We congratulate the pioneer work of these authors in Brazil to consistently show that laparoscopic surgery must be incorporated in the pediatric urologic armamentarium.

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EDITORIAL COMMENT

The laparoscopic technique, which is presently one of the highlights among the urological therapies and is still on the rise, especially due to its recent association with robot-assisted surgery, began, in the field of Urology, with uropediatrics. The first and most significant studies written about laparoscopy in Urology were done with children that had cryptorchidism. In the early 90's, the laparoscopic technique started being used in ablative procedures in children. Further ahead, in the late 90's, the laparoscopic technique was successfully used in reconstructive procedures, especially in pyeloplasty. More recently, the same

authors who are now presenting a respectable number of cases of renal surgeries in children, have already shown significant results in Wilms' tumor surgery.

In this study, the authors presented a significant number of cases of renal procedures in children, most of which were ablative, with outstanding results. In fact, the results are so good that presently their department uses laparoscopic surgery as the first indication for renal surgery in children, whereas open surgery is the exception.

It is worth mentioning the authors' preference for the transperitoneal approach, which was used in 140 out of 144 cases. Personally, I believe that the retroperitoneal or transperitoneal approach could have been randomly indicated in most of these cases, depending only on the surgeon's personal preference. There is no evidence that one approach is better that the other for most cases of renal and adrenal surgery.

I would like to challenge the authors of this excellent study to repeat their experience with the retroperitoneal approach.

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International Braz J Urol Vol. 34 (6): 749-757, November - December, 2008

Changes in Parents' and Self-Reports of Behavioral Problems in Brazilian Adolescents after Behavioral Treatment with Urine Alarm for Nocturnal Enuresis

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ABSTRACT

Purpose: Compare parents' reports of youth problems (PRYP) with adolescent problems self-reports (APSR) pre/post behavioral treatment of nocturnal enuresis (NE) based on the use of a urine alarm.
Materials and Methods: Adolescents (N = 19) with mono-symptomatic (primary or secondary) nocturnal enuresis group treatment for 40 weeks. Discharge criterion was established as 8 weeks with consecutive dry nights. PRYP and APSR were scored by the Child Behavior Checklist (CBCL) and Youth Self-Report (YSR).
Results: Pre-treatment data: 1) Higher number of clinical cases based on parent report than on self-report for Internalizing Problems (IP) (13/19 vs. 4/19), Externalizing Problems (EP) (7/19 vs. 5/19) and Total Problem (TP) (11/19 vs. 5/19); 2) Mean PRYP scores for IP (60.8) and TP (61) were within the deviant range (T score ≥ 60); while mean PRYP scores for EP (57.4) and mean APSR scores (IP = 52.4, EP = 49.5, TP = 52.4) were within the normal range. Difference between PRYP' and APSR' scores was significant. Post treatment data: 1) Discharge for majority of the participants (16/19); 2) Reduction in the number of clinical cases on parental evaluation: 9/19 adolescents remained within clinical range for IP, 2/19 for EP, and 7/19 for TP. 3) All post-treatment mean scores were within the normal range; the difference between pre and post evaluation scores was significant for PRYP.
Conclusions: The behavioral treatment based on the use of urine alarm is effective for adolescents with mono-symptomatic (primary and secondary) nocturnal enuresis. The study favors the hypothesis that enuresis is a cause, not a consequence, of other behavioral problems.

Key words: *nocturnal enuresis; adolescent; evaluation studies; treatment outcome*
Int Braz J Urol. 2008; 34: 749-57

INTRODUCTION

Nocturnal enuresis (NE) is a common problem in childhood. Epidemiological studies show that 15-22% of boys and 7-15% of girls at seven years of age are bedwetters (1). These percentages lower to 1-2% among adolescents and young adults (1,2). Facing this problem the family must make a decision: wait for spontaneous remission - approximately 15% of the enuretics stop wetting the bed each year (2-4) - or seek aid to solve the problem. The negative impact of NE on both the adolescent and the family (5-8) suggests that the second option should be chosen.

Although some children do not demonstrate negative psychological consequences of NE, the majority usually disclose distressing repercussions of being a bedwetter (1,8). The wet bed changes the daily routine, which bothers mainly younger children; for older children, enuresis becomes a humiliation. Adolescents with NE feel guilty and ashamed, they

avoid social activities, and they feel different from the others (9). This indicates that older enuretics suffer more negative psychological consequences of NE.

Several researchers have studied the relationship between enuresis and psychological problems. A 15 year longitudinal study with New Zealand children investigated the relationship between nocturnal enuresis and measures of behavioral adjustment in adolescence (10). Patterns of nocturnal bladder control were evaluated once a year (from 2 to 15 years old), and psychological measures were collected at ages 11, 13 and 15. Results have shown that children who continued to wet the bed after the age of 10 as a result of either primary or secondary enuresis had more behavioral problems and attention deficit up to the age of 13, and more internalizing problems up to the age of 15 (10).

A review of the literature (11) suggests that bedwetting causes other behavioral problems, rather than the other way around. The relationship between NE and behavioral problems seems to be stronger in older enuretics, although cause and effect still have not been established (11). A study developed in China, using the Child Behavior Checklist (CBCL) as the psychological measure, showed that the later the children achieved the urine control, the higher the probabilities of parents reporting behavioral, emotional and academic problems (12).

Although the literature concerning enuresis and behavior problems is vast, the results must be accepted with caution. The criteria used to consider a child as being enuretic are usually different from one study to another, and the methodological design of studies does not always allow firm conclusions to be drawn (13,14). In addition, most studies focus on externalizing problems evaluated from only one point of view (parental evaluation of their children's behavior), thereby ignoring the internalizing problems and adolescents' self-reports.

In one of the first studies that specifically investigated internalizing problems in children with enuresis, no differences were found between self-reports of bedwetters and a control group of children without enuresis (15). However, the parents' reports of the children's behavior were different across the two groups. Parents of enuretics tended to indicate their children as having more internalizing problems ("withdrawn" and "anxious/depressive") than compared controls (15).

The importance of having multiple informants when evaluating children's behavioral problems has been emphasized by the previous researchers (15). These authors observed that overall agreement between children and parent reports was low to moderate, whereas parent-child agreement in a sample of enuretic children was moderate to good (15). Despite the fact that the information source seems to influence the severity of reported problems, clinical work and scientific studies have emphasized the necessity of including multiple informants in the diagnostic evaluation of children and adolescents (16). Apparently when parents evaluate their children, more externalizing problems are reported, while children, on self-report, point out more internalizing problems. Even though there is consensus that is important to have multiple informants during child/adolescents' assessment, the literature still has not reached a consensus on how to interpret the differences found in both reports (16).

The effects that treating enuresis has on other behavioral problems have been investigated in only a few studies. The first randomized, controlled study examining if there were changes in behavioral problems after six months of enuresis treatment with a urine alarm, desmopressin acetate or placebo found significant changes on CBCL scores for Internalizing Problems, Externalizing Problems, Social Problems, Thought Problems and Attention Problems (17). These changes occurred independently of the treatments' result and the kind of treatment offered, including placebo condition. These authors suggested that the attention, support, and reassurance inherent in participation in the study were beneficial for all children (17).

Some researchers from the Netherlands also attempted to investigate the effects of enuresis treatment on other behavioral problems (18). A reduction in mean scores on the CBCL occurred six months after treatment in the group of children who achieved success on controlling bedwetting. The most significant differences were found in mean scores on internalizing problem scales, specifically in the scale of anxiety/depression. The observed reduction on other behavior problems after a successful enuresis

treatment suggests that the other behavioral problems were a consequence of the bedwetting, not the cause of this bio behavioral problem. This hypothesis has been supported by several studies (11,15,18).

Apparently, enuresis treatment has the effect of reducing the frequency, and/or the intensity, of other behavioral problems, although there is no consensus whether it is necessary to achieve success in the enuresis treatment to obtain the reductions. Considering the fact that there are few studies that analyze general behavioral changes after treatment for nocturnal enuresis, and that it is important to have multiple informants in the assessment of child and adolescents problems, the present study was designed to compare parents' reports on youth problems (PRYP) with adolescent problems self-reports (APSR) before and after a behavioral treatment based on the use of urine alarm for nocturnal enuresis. We hypothesized that, since enuresis seems to be a cause of other behavioral problems, adolescents' self-report and parents' reports would indicate a reduction on behavioral and emotional problems following treatment for NE.

MATERIALS AND METHODS

A total of 19 youths - 13 boys and 6 girls - (age ranging from 11 to 16, average 12.32 years, SD = 1.83 years) participated in this study. The psychologist used a screening interview to evaluate the type of bedwetting presented by participants. All participants met the criteria for mono-symptomatic nocturnal enuresis established by the International Children's Continence Society (19): involuntary voiding of urine during sleep in children without other lower urinary tract symptoms and without history of bladder dysfunction. Most adolescents (16/19) had primary nocturnal enuresis; although three (two boys and one girl) were diagnosed with secondary enuresis, since they had been dry for a period of six months or more, and then started bed wetting again. The majority (15/19) had previously undergone pharmacological treatment , but had not ceased wetting the bed. The number of wet nights before treatment ranged from 2 to 7 wet nights per week (average 5.42 wet nights per week, SD = 1.84).

To evaluate behavioral problems in young adolescents, the rating from the Achenbach System of Empirically Based Assessment (ASEBA) was chosen. This system is used worldwide in different contexts, including medical clinics, psychological clinics, and in research (20). Moreover, the ASEBA is the most widely used and researched system of its kind, with some 6,000 publications reporting findings in 67 different cultures (20). Since several researchers in the enuresis field have used the ASEBA to evaluate behavioral problems, it was chosen to assess the parent's reports on youth's problems (PRYP) and the adolescent's problems self-reports (APSR) in the current study.

The parents completed the "Child Behavior Checklist for ages 4 to 18" (CBCL/4-18) (21), which yield three broadband scales of Internalizing (IP), Externalizing (EP) and Total Problems (TP). T-scores of 60 or higher were considered to be deviant consistent with the questionnaires of authors who suggest combining the clinical range and the borderline range to establish deviance.

In addition, the participants completed the "Youth Self-Report" (YSR) (22). This self-report questionnaire has problem items generally parallel to those of the CBCL. The scores derived and the deviance cut points are similar to those for the CBCL.

After this first evaluation process (pre attendance assessment), the treatment was started. Parents and participants had to agree that while they were involved in this treatment, they could not receive any other treatment. The behavioral treatment based on the use of urine alarm was chosen either due to the high success rate and low relapse rate reported for this device in the literature, or to the low costs involved (2). The adolescent, the family, and the psychologist worked together to achieve dry nights, since behavioral treatment for bedwetting requires concerted and cooperative effort from the entire family (2). The treatment, based on the program proposed by Arthur C. Houts (2), involved attending weekly sessions of behavioral treatment, which focused on several procedures well described by Blackwell (23), such as: explaining the nature of enuresis, following treatment instructions for use of the urine alarm, cleanliness training, retention control training, solving daily problems, recording dry/wet nights and control

of drinking diuretic beverage before bedtime (23). After achieving 14 consecutive dry nights we added the over learning procedure (2).

Eight weeks without wet nights were considered for discharge.

The treatment was planned to last 40 weeks. After that period, regardless of the achieved NE result, parents and adolescents were asked to complete the questionnaires (CBCL and YSR, respectively) a second time (post treatment assessment).

Approval by University Ethics Committee was obtained, and a formal written consent was signed by the participants. All questionnaires were scored using the software ADM (Assessment Data Manager) (24), developed by Achenbach et al. for this purpose. Statistic analyses were done using the software SPSS 13.0 for Windows.

RESULTS

Enuresis Control

All participants achieved at least 2 weeks with consecutive dry nights, and the majority (16/19) remained dry for 8 consecutive weeks and were discharged.

Behavioral Problems

Figure-1 shows the proportion of cases in the deviant range before and after treatment as scored by parents and youths.

Although more adolescents achieved the deviant range on parent's report (13/19 on IP, 7/19 on EP, and 11/19 on TP) than on youths' self-report (4/19 on IP, 5/19 on EP, and 5/19 on TP), no statistical difference was found between observers in the number of clinical cases for IP ($\chi^2(1, N = 19) = 0.101$, $p = 0.750$), EP ($\chi^2(1, N = 19) = 0.827$, $p = 0.363$), and TP ($\chi^2(1, N = 19) = 1.360$, $p = 0.243$) before treatment. The number of participants scoring within the deviant range on CBCL and the YSR decreased on post-treatment rates, but were still higher according to parent's reports on IP (9/19), EP (2/19), and TP (7/19) than adolescents' reports on IP (4/19), EP (1/19), and TP (3/19). Chi-square tests were used to determine if the difference in number of clinical cases was significant after treatment. No statistical difference between

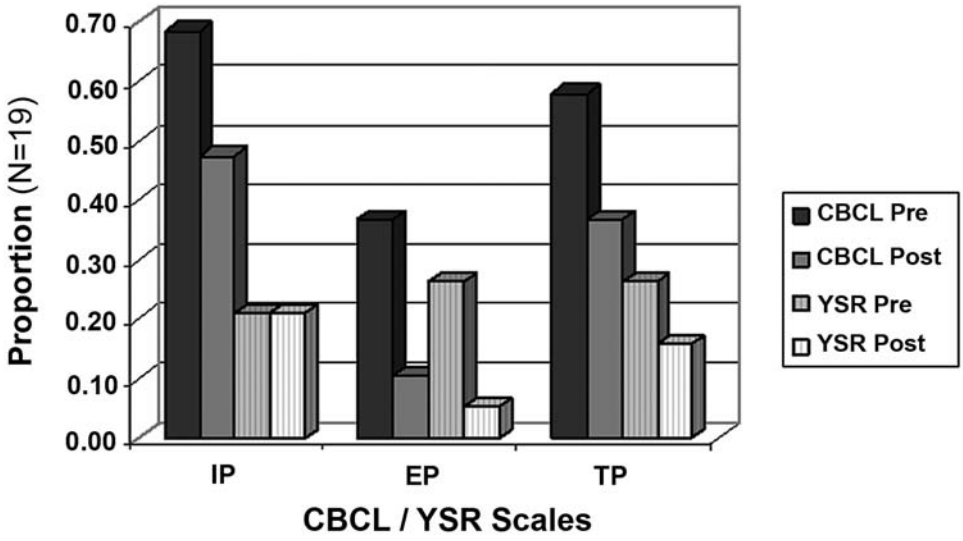

Figure 1 – *Proportion of adolescents within clinical range (pre and post treatment data) according to parents' reports on CBCL and to youths' reports on YSR. IP = Internalizing Problems Scale; EP = Externalizing Problems Scale; TP = Total Problems Scale.*

observer was found for IP ($\chi^2(1, N = 19) = 0.281$, $p = 0.596$), EP ($\chi^2(1, N = 19) = 0.124$, $p = 0.725$), and TP ($\chi^2(1, N = 19) = 2.078$, $p = 0.149$).

Average T Score Evaluation

Figure-2 shows the average T score obtained by participants (pre/post treatment data).

ANOVA with repeated measures was used to compare the mean T scores obtained with the CBCL and the YSR. Before treatment, the mean score obtained from parents report (CBCL) was significantly higher than the mean score obtained for youths' self-report (YSR) for IP (Wilks' $\lambda = 0.658$, $F(1,18) = 9.340$, $p = 0.007$), EP (Wilks' $\lambda = 0.730$, $F(1,18) = 6.662$, $p = 0.019$), and TP (Wilks' $\lambda = 0.549$, $F(1,18) = 14.774$, $p = 0.001$). Mean CBCL IP and TP scores were in the deviant range (T score ≥ 60), whereas mean CBCL EP score, and mean YSR scores were within the normal range (T score < 60).

After treatment, CBCL scores were still significantly higher that YSR scores for IP (Wilks' $\lambda = 0.632$, $F(1,18) = 10.472$, $p = 0.005$), EP (Wilks' $\lambda = 0.742$, $F(1,18) = 6.257$, $p = 0.022$), and TP (Wilks' $\lambda = 0.619$, $F(1,18) = 11.1$, $p = 0.004$), although both CBCL and YSR scores were below the deviant range (T score < 60).

Single ANOVA with repeated measures was used to investigate the differences between parents' reports (PRYP) on youth's problems before and after treatment, and adolescents' problems self-report (APSR) before and after treatment. Results are shown on Table-1.

Table-1 shows that mean CBCL IP, EP and TP scores after treatment were significantly lower than pre-treatment scores, which indicates that parents reported fewer problems after their children had gone through behavioral treatment based on the use of urine alarm. No significant differences were found on the youths' report when pre-treatment and post-treatment scores were compared.

COMMENTS

Treatment with a urine alarm is the most frequently adopted behavioral intervention for bed-

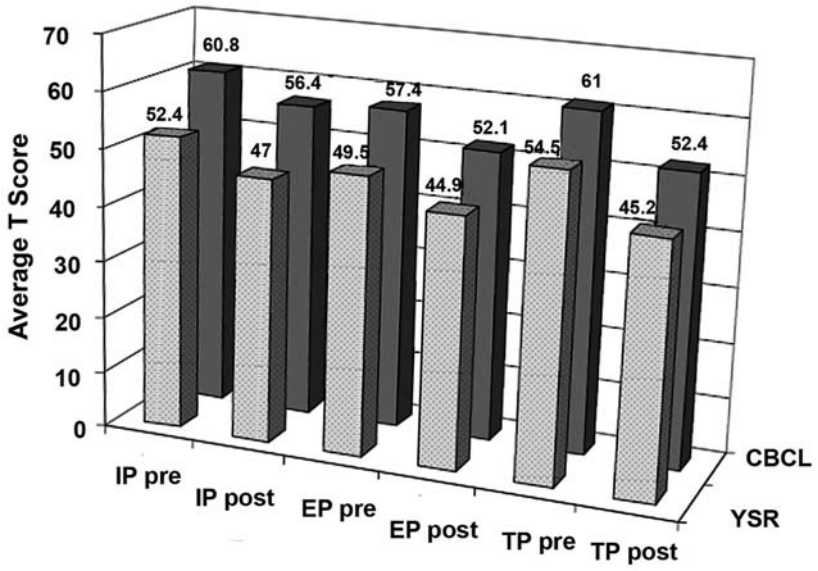

Figure 2 *– Adolescent average T scores obtained by parental (CBCL) and self (YSR) reports; pre and post treatment data. IP = Internalizing Problems Scale; EP = Externalizing Problems Scale; TP = Total Problems Scale.*

Table 1 – *Differences between evaluation data pre and post treatment.*

	Pair	Single ANOVA with Repeated Measures
CBCL - Parents' reports	IP Pre vs. IP Post	Wilks' $\lambda = 0.791$, $F(1,18) = 4.758$, $p = 0.043$*
	EP Pre vs. EP Post	Wilks' $\lambda = 0.789$, $F(1,18) = 4.826$, $p = 0.041$*
	TP Pre vs. TP Post	Wilks' $\lambda = 0.743$, $F(1,18) = 6.234$, $p = 0.022$*
YSR - Youth's reports	IP Pre vs. IP Post	Wilks' $\lambda = 0.847$, $F(1,18) = 3.254$, $p = 0.088$
	EP Pre vs. EP Post	Wilks' $\lambda = 0.822$, $F(1,18) = 3.893$, $p = 0.064$
	TP Pre vs. TP Post	Wilks' $\lambda = 0.869$, $F(1,18) = 2.719$, $p = 0.117$

** $p \leq 0.05$. IP = internalizing problems; EP = externalizing problems; TP = total problems.*

wetting (2,5,25) and has shown high efficacy. The success rate reached in our study (84.21%) is superior to the success rate found in the enuresis literature, which is 60% to 70% of the cases (25). However, the comparison between studies is very difficult, since the literature has reported different inclusion criteria and success criteria (13,14). If we considered 14 consecutive dry nights, the most widely used success criterion found in the literature (14), we would have achieved 100% success. It is likely that the treatment offered (behavioral treatment based on the use of urine alarm) is a factor that helped to achieve our high rate of success. Most treatments with urine alarm do not have a weekly session to monitor the alarm use. The psychologist motivated and helped the parents and the adolescents to accurately follow the procedure - which is very important to achieve success using the urine alarm -, and used social positive reinforcement as a consequence for all appropriate behaviors. In addition, the other procedures that were followed during the use of the urine alarm may have also interfered in the final result, although more data is needed to sustain this statement. The over learning procedure and the criteria for discharge of 8 consecutive weeks with dry nights might have reduced the relapse rate, but only follow up studies can confirm this hypothesis.

Among the vast literature regarding behavior problems and nocturnal enuresis, there are few reported studies focusing on internalizing problem changes after enuresis treatment, and fewer studies using both adolescents' and parents' reports. The present study addresses this gap in the literature. The results indicate that enuretic adolescents, even before treatment, did not report scores in the deviant range on YSR Internalizing Problems, Externalizing Problems and Total Problems scales. Parents' reports were significantly different from youth's self-reports: parents judged their enuretic children to be within the deviant range for Internalizing and Total Problems before treatment. These data are similar to those reported in a Belgian study (15): the children who participated in the Belgian study did not report more internalizing problems than control children did. However, parents' reports on the CBCL indicated that enuretic children have higher anxious/depressed and withdrawn scores than control children. Both Brazilian and Belgian results indicate that parents are more likely to evaluate their children as having other behavioral problems (besides enuresis) than bedwetting.

One explanation for the differences found between parents' reports and adolescents' self-reports might be that adolescents do not want to disclose everything, or that they try to deny the problems they are facing (16). Another explanation could be that parents evaluated their children as worst than they really were, imagining that this was the way to obtain treatment. It is also possible that, as the enuresis problem seems to make parents pay more attention on their children, they could also perceive their children's behavioral problems greater or more frequent than other parents who are not so focused on their children. We cannot forget that adolescence is a "gap period" when conflicts between parents and their children increase, and differences in their perceptions on several topics are very common. It is also important to note that par-

ent-adolescent agreement on the CBCL-YSR in the U.S. normative sample was only 0.29 (26). This low agreement level has repeatedly been documented in studies that compare parents' reports and adolescent self-reports (16).

Even though the literature reports that on parental evaluation, adolescents achieve higher scores on externalizing problems, and on self-report, they indicate more internalizing problems (16), we did not find results indicating that type of difference. In fact, parents reported more internalizing problems than externalizing problems when they evaluated their youths.

Although there was a visible decrease in the mean score of the YSR IP, EP and TP following treatment, the difference was not significant. At both time points, mean YSR scores were in the normal range, indicating that enuretic adolescent did not evaluate themselves as having other behavioral problems, besides enuresis.

Similar to the results found in Canada (17), we found declines in CBCL IP, EP and TP scores post behavioral treatment based on the use of urine alarm for nocturnal enuresis. Results in the same direction were also found in the Netherlands (18). In the Dutch study, children who overcame enuresis seemed to have less internal distress, fewer problems with other people, and were less anxious and/or depressed after treatment based on parents' reports using the CBCL.

It is likely that the information and support offered during treatment were beneficial to the participants. All adolescents showed significant declines in bedwetting, even though the decline in YSR scores was not significant. This was probably because YSR scores were relatively low before treatment began. It is also possible that parents' satisfaction with the achieved control of NE as a result of treatment led them to view their adolescents more favorably on the CBCL. In future research, it will be important to determine if the treatment gains in NE and CBCL scores persisted after one year. Our data provide additional support for the hypothesis that behavioral/emotional problems are often a consequence of bedwetting rather than cause of enuresis (e.g. 11,15,18).

One limitation of the present study is the small number of participants, which resulted in low power to detect effects. Our study certainly would have been enhanced if we had had a larger number of participants. In addition, the use of rating scales rather than diagnostic assessments was a further limitation. A no-treatment control group would also have contributed to our study. This would have allowed comparison between behavioral changes in enuretic adolescents who had had treatment access versus those who did not receive treatment. Based on our data, we cannot answer the question about whether it is necessary to achieve success in enuresis treatment to have changes on other behavioral problems, since virtually all our participants achieved control over bedwetting (at least 14 dry nights). This study as not able to replicate the study performed in the Netherlands (18) that compared behavioral changes that occurred in the group that achieved success and the group that did not achieved success with the enuresis treatment because in our study all participants achieved at least two consecutive weeks with dry nights, the most widely used success criterion (14).

CONCLUSION

The behavioral treatment based on the use of urine alarm for enuresis was effective for ceasing bedwetting in adolescents with mono-symptomatic (primary and secondary) nocturnal enuresis. Since this treatment also seems to produce a positive effect on other behavioral problems, or on the parental report of these behavioral problems, it is important to advise parents to seek treatment for NE for their adolescents. The hypothesis that enuresis is a cause, not a consequence of other behavioral problems, was supported by our data.

ACKNOWLEDGMENT

The study was supported by grants from FAPESP, CNPq and USP. Dr. Leslie A. Rescorla provided critical discussion on the manuscript.

CONFLICT OF INTEREST

None declared.

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Accepted after revision:
July 2, 2008

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EDITORIAL COMMENT

Many studies focus on the relationship between enuresis and psychological problems/psychopathology. However, most of these studies have a cross-sectional design, which makes deductions about causality very difficult. The current study makes an important contribution to this field of research since it consists of two time measurements: before and after treatment. This study design enables the authors and readers to deduct some well-founded hypotheses on causality. Nevertheless, I believe the manuscript could benefit considerably from the following comments.

An important limitation for this study is also the small sample size (from a statistical point of view). Also, whether alarm treatment is effective depends heavily on the etiology of enuresis. The current statement is not a general conclusion from this study.

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EDITORIAL COMMENT

This is an uncontrolled clinical study examining the effect of successful enuresis alarm treatment on psychological functioning (through parental and self-perception) with a small sample (n=22) of adolescents with nocturnal enuresis.

The paper specifically seeks to explore both the difference in opinion between parent and youngster with respect to behavior; and an analysis of change in psychological functioning before and after treatment with the enuresis alarm.

The paper is very clear and highlights the importance of understanding behavior from both the parent and protagonist's perspective. I also like how the authors have defined mono-symptomatic nocturnal enuresis. In all I think the paper would be a welcome addition to the literature.

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International Braz J Urol Vol. 34 (6): 758-764, November - December, 2008

Electromotive Drug Administration for Treatment of Therapy-Refractory Overactive Bladder

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ABSTRACT

Purpose: Evaluate the benefits of electromotive drug administration (EMDA) as an alternative technique in patients with chronic overactive bladder in terms of improvement of symptoms, quality of life, and sexuality.
Material and Methods: A total of 72 patients with therapy-refractory overactive bladder according to the ICS (International Continence Society) definition, were treated by EMDA. The regimen consisted of three treatment cycles, each with 3 instillations at 2-week intervals. The solution instilled consisted of 100 mL 4% lidocaine, 100 mL distilled water, 40 mg dexamethasone, and 2 mL epinephrine. Peri-interventionally, a urine test and close circulatory monitoring were performed. All women underwent urodynamic testing and cystoscopy and kept a voiding diary. A comprehensive history was obtained, a quality of life questionnaire administered, and a gynecologic examination performed before initiation of therapy. The women underwent follow-up at 12 months after the end of therapy.
Results: The patients had a mean age of 63 (± 11.2) years. Bladder capacity improved significantly by 109 mL (± 55 mL) in 51 (71%) patients (p = 0.021). The number of micturitions/day decreased significantly to 7 (± 2) (p = 0.013). Quality of life was improved in 54 patients (75%); p = 0.024) and sexuality in 39 (54%); p = 0.020).
Conclusions: The results suggest that EMDA can improve both quality of life and sexuality in patients with therapy-refractory chronic overactive bladder.

Key words: *overactive bladder; therapy; quality of life; sexuality*
Int Braz J Urol. 2008; 34: 758-64

INTRODUCTION

Overactive bladder (OAB) has a socioeconomic impact that is comparable to that of diabetes mellitus. As life expectancy is increasing, this condition will become even more important in the future. In the new classification of the International Continence Society (ICS) (1), an overactive bladder is defined as a complex of symptoms comprising frequency, nocturia, and sudden compelling desire to void with or without urge incontinence. OAB has a prevalence of approximately 17%. The etiology of OAB comprises neurogenic and non-neurogenic detrusor overactivity and detrusor hypersensitivity; also discussed is urothelial dysfunction (2). Most affected patients seek medical advice very late, at a time when the symptoms have progressed to a stage where permanent treatment is required. Compliance is poor in most patients who have already tried a variety of therapies that failed or led to minor improvement at best. Most approaches rely on medications. Comparison of the effects of different agents is difficult because the reported studies investigating these therapies differed in design and patients population investigated. Moreover, physiotherapeutic education and behavioral training or bladder drill are offered either alone or in combina-

tion with medical treatment. After these therapeutic options fail to cure or improve OAB, physicians and patients are often at a loss. The cost for incontinence aids increases and many of the patients in whom all therapeutic options have been tried are on long-term sick leave or incapable of gainful employment. We therefore intended to offer a treatment that has previously been established and has been shown to be effective in patients diagnosed with OAB. Electromotive drug administration (EMDA) combines iontophoresis and electrophoresis for targeted delivery of drugs to deep tissue layers. This is achieved by means of an electrical field created between electrodes. Passive diffusion overcomes some of the limitations of conventional drug administration and achieves a higher local concentration of the drug while reducing possible toxic effects. At the same time, EMDA can be used to improve bladder capacity by means of bladder distension without the need for anesthesia. Our aim was to establish an effective, permanent or repeatedly applicable therapy for patients with chronic OAB while at the same time minimizing adverse effects.

In the study presented here, EMDA therapy was used in 72 patients with overactive bladder.

Treatment consisted of a stepwise approach. Patients were initially treated with anticholinergics. If two anticholinergics failed, patients were treated with uropol-S® instillation. Alternatively, electrostimulation with a current of 20 Hz or less combined with bladder training was offered. If this also failed, patients underwent urodynamic and cystoscopic diagnostic workup. Patients in whom the diagnosis of OAB was confirmed were then treated by EMDA. The aim of our study was to show that EMDA therapy improves the patients' quality of life and sexuality.

MATERIALS AND METHODS

A total of 72 patients with therapy-refractory overactive bladder according to the definition of the ICS (3) received EMDA treatment. Of the 85 patients initially eligible for the study, 13 (20%) were excluded from treatment because they had abnormal pelvic floor electromyography (EMG) findings.

Inclusion Criteria: Patients were included if they had a history of OAB persisting for over 24 months and therapeutic attempts with at least two different anticholinergic medications and at least 6 months of physiotherapy without improvement or cure of symptoms: frequency (voiding more than 8 times a day), nocturia (voiding more than once a night), and urge incontinence. The voiding frequency was determined by means of a voiding diary the patients kept for three days. All patients underwent urodynamic testing before and after treatment. The following parameters were determined: first urge to urinate (normal: one third of total bladder capacity), bladder capacity (normal: > 300 mL), and positive detrusor contractions. Presence of residual urine was an exclusion criterion. Residual urine was determined by ultrasound and clinically by means of catheterization during urodynamic testing. A cystoscopy was performed in patients who had their last cystoscopy more than 6 months earlier.

A vaginal examination served to rule out pelvic organ prolapse and to evaluate the mucosa (4). Introital ultrasound was performed in a standardized manner (5) and served to verify abnormal findings (e.g., exclusion of urethral diverticula, tumors). Each patient was administered a quality of life (6) and sexual exploration questionnaire (7) before and after treatment. Quality of life was assessed using the validated Kings Health questionnaire. The questionnaire on sexuality was compiled by the Institute for Sexual Medicine of Humboldt University in Berlin and is also a validated measuring instrument.

Voiding frequency, nocturia, first urge, bladder capacity, quality of life, and sexuality were compared before and after treatment. Pad counts were not done because the results were not comparable as patients use a diversity of products.

Each patient received three treatment cycles each with three instillations at two-week intervals (± 3 days). The solution instilled consisted of 100 mL 4% lidocaine hydrochloride (NaCl-free), 100 mL distilled water, 40 mg dexamethasone sodium phosphate, and 2 mL epinephrine. Close circulatory monitoring was performed peri-interventionally (6 times a day) and a urine test was done. Patients were hospitalized for three days.

The EMDA system used in the study consists of a control unit (Physionizer® 30, UROMED) and a catheter electrode with a diameter of 16F and a

shaft length of 40 cm. The electrode (CE-DAS® UROGENICS® /Ag 9701) was inserted and then blocked by means of a balloon inflated with 3 mL of air. The bladder was rinsed with distilled, sterile water and drained. Bladder tolerance was then determined as the level at which symptoms occurred. The medications instilled had a total volume that was 5-10 mL below the bladder capacity at which the individual patient experienced symptoms. Two patch electrodes were applied to the abdomen and the Physionizer® was connected to the catheter and the patch electrodes. Patients were treated for 20-25 min with application of 15-25 mA. Current was increased at a rate of 30-60 uA/sec. The frequency was 2.5 kHz. The current applied was direct current with rectangular impulses. Absolute contraindications were urinary tract infection before therapy, allergy/intolerance of local anesthetics, massive intravesical bleeding, pregnancy, patients taking medications of the group of monoaminoxidase inhibitors and cardiac pacemaker.

Patients underwent follow-up 12 months after the last treatment.

Statistical analysis was performed by the Institute of Dr. Matthias Koch-Moeck using MedCalc 9.0.

RESULTS

History and Diseases

The patients had a mean age of 63 (± 11.2) years. With a Body Mass Index of 31 (± 4.1), the majority of patients were overweight. Overweight was found to correlate with the symptoms of OAB.

Fifteen patients (21%) had a history of anti-incontinence surgery and 19 (27%) had undergone prolapse surgery. There was no correlation with OAB. Five patients were nulliparae. The number of deliveries in the other patients ranged from 1 to 7. The number of deliveries had no effect on the severity of symptoms. Eighteen patients with type II diabetes mellitus (25 %) had no EMG changes of the pelvic floor. Twelve patients (17%) had neurological disorders that did not correlate with their urogynecologic diseases (Figures-1 and 2).

Eighteen patients (25%) were previously treated by electrostimulation, 46 (64%) by a combination of electrostimulation and biofeedback (Table-1).

Clinical Examination

Pelvic floor muscle contraction was assessed using the Oxford grading system (8). The average strength was 2 (± 2) and an association was found between poor strength and premature first urge ($p = 0.0003$).

The gynecologic examination did not show any prolapse in any of the patients (ICS stage 0). Fifty-one (71%) patients had a pH of 4.2 (± 0.2), indicating good estrogenization, while 21 (29 %) had poor estrogenization with a pH of 5.5 (± 0.1). The patients with poor estrogenization were prescribed ovestin ovula pessaries (for vaginal application every 3 days for 3 months). Introital ultrasound did not show any significant pathology.

Table 1 – *Medications before start of electromotive drug administration (EMDA) treatment.*

Medication Before Start of EMDA Treatment	Number / Percentage
Trospium chloride	32 / 44%
Tolterodine	34 / 47%
Oxybutynin	19 / 26%
Oxybutynin transdermal patches	15 / 21%
Propiverine	19 / 14%
Sodium chondroitin sulfate (uropol-S)	72 / 100%

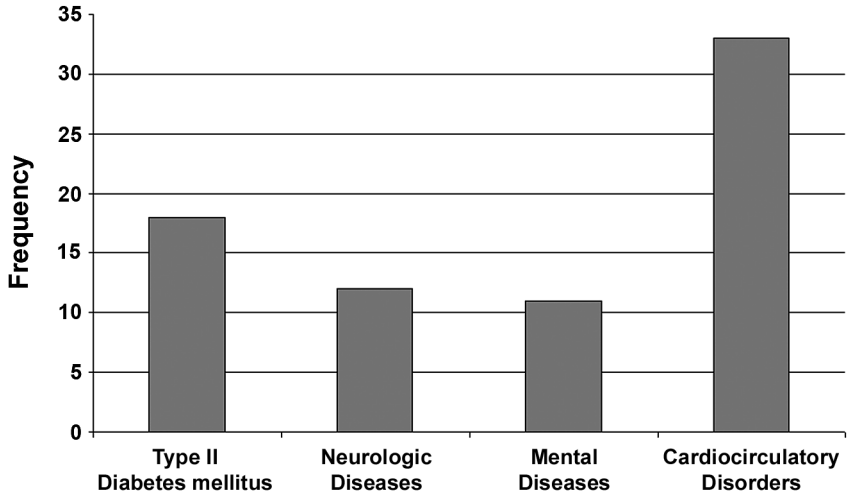

Figure 1 – *Concomitant diseases. There was no significant association between concomitant diseases and outcome of treatment.*

Urodynamic Testing

The average bladder capacity was 185 mL (± 32 mL) and patients had an average voiding frequency of 16 (± 3) times a day. In 33 patients, bladder capacity was significantly improved by 110 mL (± 25 mL) ($p = 0.0001$). Voiding frequency decreased significantly to 7 (± 2) times a day ($p = 0.003$). Nineteen patients (26 %) had detrusor overactivity, which was terminal in

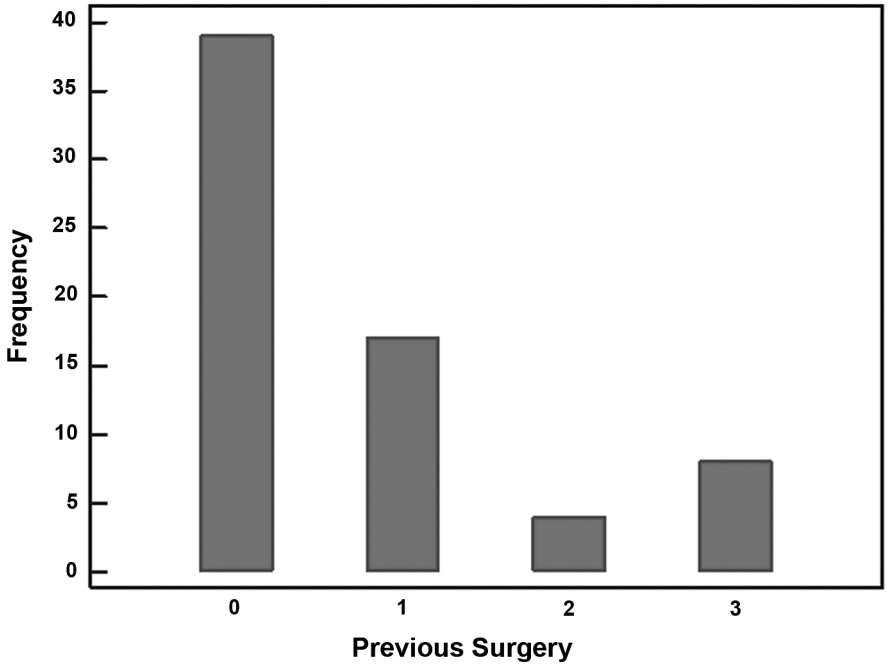

Figure 2 – *Previous surgery. 0 = none; 1 = TVT; 2 = botox injection; 3 = prolapse surgery.*

15 of them (21 %) and phasic in the other 4 patients (30.8%). In 7 (37%) of the 19 (26%) patients, it was not possible to evaluate involuntary detrusor contraction following treatment. The first urge was premature in 41 (57%) patients before treatment versus 18 (25%) after treatment (Tables-2 and 3).

No abnormal residual urine volumes were identified either sonographically or clinically.

Nocturia, Quality of Life, and Sexuality

Nocturia showed a tendency to improve from 5 (± 2) to 2 (± 1).

Quality of life was improved in 54 patients (75%); patients ($p = 0.002$). Thirty-nine (54%) patients had improved sexuality ($p = 0.001$) in terms of sexual sensations and sexual satisfaction. Quality of life was unchanged in 15 (21%) and worsened in three (4%), Figure-3.

Adverse Effects

Twelve of the women (17%) developed reactive hypertension during treatment, which returned to normal without intervention.

Signs of dysuria and hematuria were observed in a total of 21 patients (29%). Urinary tract infection occurred in 10 women (14%) and was treated with a 7-day regimen of 250 mg ciprofloxacin (2 x 1 tablet), followed by a urine test. One patient developed urinary retention, which disappeared after she was catheterized twice.

COMMENTS

Although the number of patients investigated in our study is still too small to draw any general conclusions, our data clearly suggests that the symptoms of overactive bladder tend to markedly improve using electromotive drug administration (EMDA) for treatment. Our therapeutic approach cannot be compared with other currently available treatments using agents such as oxybutynin, protamine sulfate, and dimethyl sulfoxide (9,10) because these procedures use very different modes of administration.

The combination of drugs we used was specifically selected to control urge and pain as well as chronic inflammation of bladder tissue, which is present in most affected patients. The approach used here allows simultaneous bladder distension for improving bladder capacity without the need for anesthesia. We attribute the improvement observed in our patients to the drugs administered by iontophoresis (EMDA) and bladder distension since they did not receive additional anticholinergic treatment or physical therapy. From a strictly scientific point of view, our study population should have been compared with a con-

Table 2 *– Results of urodynamic testing. There was significant improvement in the urodynamic parameters investigated.*

	Before	**After**
Premature first urge	41	18
Detrusor contraction	19	7
Bladder capacity (mL)	185 ± 32	110 ± 25

Table 3 *– Comparison of group A (sensory urge) and group B (detrusor overactivity) The only significant difference in post-therapeutic improvement was found between the two groups for voiding frequency.*

	Bladder Capacity	**Voiding Frequency** (per day)	**N of Involuntary Loss of Urine**	**Involuntary Loss of Urine** [< 5 pro Tag]
(A) Sensory urge (41)	281 mL	9	18	23
(B) Detrusor overactivity (19)	264 mL	5	11	8

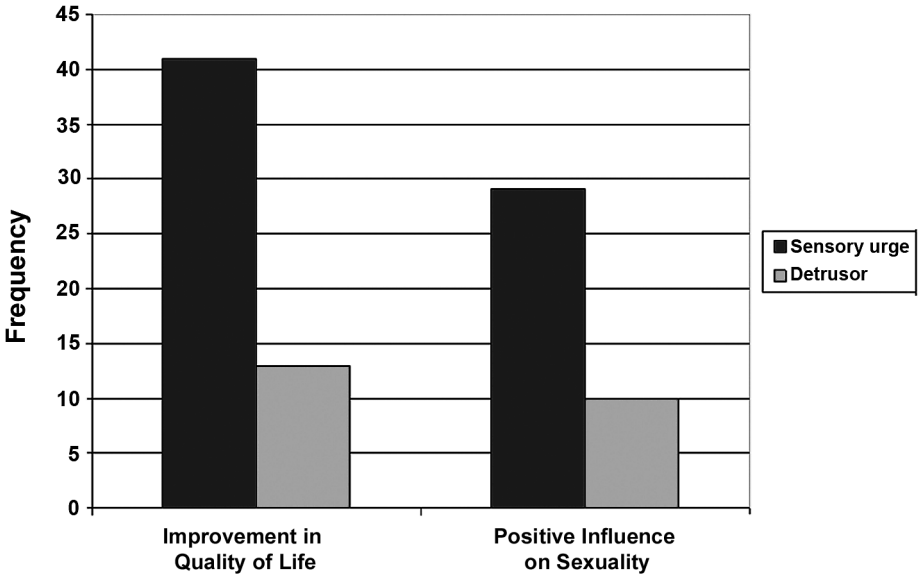

Figure 3 *– Post-therapeutic quality of life and sexuality in group A (sensory urge) and group B (detrusor overactivity). Significant improvement in quality of life was observed.*

trol group receiving placebo. Ethical considerations precluded this approach because most of our patients had very long histories of chronic disease. Investigation of a larger group of patients might provide sufficient evidence for the effectiveness of EMDA. Both above-mentioned effects of this therapeutic approach were observed in our patients: voiding frequency was reduced in our patients while bladder capacity was markedly increased. These effects in turn improved quality of life in general as well as sexuality (less involuntary urine loss during and around intercourse, greater enjoyment of sexual sensations, more frequent orgasms). We also found that an abnormally high BMI tended to impair pelvic floor function, suggesting that affected patients should be helped to lose weight by means of dietary therapy adapted for this population. Analysis of the medications and physiotherapeutic approaches used in the patients before EMDA treatment revealed no association with outcome. However, a slightly improved response rate was seen in the patients who were treated with oxybutynin transdermal patches (kentera®) but the difference was not significant. The adverse effects seen in our patients were moderate and comparable to those reported in the literature (11). However, the circulatory effects associated with this kind of treatment suggest that closer cardiologic workup should be performed prior to treatment. The current pre-therapeutic diagnostic workup has already been supplemented by an ECG and a medical consultation. Circulatory monitoring is needed in all cases. Quality of life was unchanged in 15 (21%) and worsened in three (4%).

Three patients (4%) who did not report improvement had poor compliance in that the treatment sessions were performed at very irregular intervals. We assume that this reduced the efficiency of EMDA but have no definitive evidence because the time differences were too small (± 3 days).

OAB is not a normal condition in adults regardless of age, sex, and degree of mobility. While not life-threatening, the condition is associated with an unnecessary economic burden and may lead to isolation, depression, embarrassment, and low self-esteem of affected individuals. The results presented here suggest that very good outcome can be achieved with EMDA, which allows local drug administration without severe adverse effects. Our results deserve to be further corroborated in larger studies inves-

tigating EMDA as second-line treatment option in patients with overactive bladder, since we observed an improved quality of life during one-year follow-up. Therefore, we think it is very promising to continue treatment, assess intermediate-term results, and adjust the therapeutic approach as needed.

CONFLICT OF INTEREST

None declared.

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Accepted after revision:
July 22, 2008

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Neurourology
International Braz J Urol Vol. 34 (6): 765-771, November - December, 2008

Mixed Incontinence: Does Preoperative Urodynamic Detrusor Overactivity Affect Postoperative Quality of Life After Pubovaginal Sling?

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ABSTRACT

Objective: Our purpose was to determine if women with mixed urinary incontinence (MUI) and urodynamic detrusor overactivity (DO) have less improvement in urinary symptoms after pubovaginal sling surgery (PVS), compared to MUI without DO.
Materials and Methods: Women with preoperative MUI symptoms prior to PVS were identified through retrospective review. DO was defined as a symptomatic 5 cm H_20 detrusor pressure or greater rise during urodynamics. MUI patients with and without DO before PVS were divided into Groups A and B, respectively. All patients had returned a completed Urogenital Distress Inventory 6 (UDI-6) questionnaire and a 3-day diary of pad usage before surgery and at each postoperative visit. Study endpoints included change in total UDI-6 score, and change in number of pad use/day after PVS.
Results: 73 patients were identified, 31 in Group A and 42 in Group B. Mean follow-up after PVS was 15 and 16 months, respectively (p = 0.59). Preoperative total UDI-6 scores were 11.8 and 12.7 (p = 0.30) for Group A and B. Mean changes in total UDI-6 after PVS were - 8.0 and - 10.2 (p = 0.030), respectively. After PVS, both groups reported similar mean reduction in pad/day usage from preoperative baseline (-2.57 vs. --2.49, p = 0.83). There were no differences between the groups when comparing demographic, urodynamic, or operative data.
Conclusion: MUI patients had improved continence and quality of life after PVS. However, MUI patients with DO had less improvement in UDI-6 scores after PVS, despite a similar reduction to pad use/day.

Key words: *urodynamics; urinary incontinence; urge incontinence; suburethral slings*
Int Braz J Urol. 2008; 34: 765-71

INTRODUCTION

Mixed urinary incontinence (MUI) is clinically defined by as "involuntary leakage associated with urgency and also with exertion" (1). In theory, the urge incontinence component of this definition is likely caused by an uninhibited bladder contraction. During urodynamic studies, uninhibited contractions, defined as Detrusor Overactivity (DO), are identified through symptomatic rises in the detrusor pressure during the study filling phase (2). Interestingly, many women with clinically defined MUI do not demonstrate DO during urodynamic studies (3). Consequently, the relationship between DO and clinical symptoms is often conflicting and has not been fully delineated.

Many women with symptomatic MUI are offered surgical therapy. However, surgical cure rates

for the MUI patient are highly variable and range from 60 - 97% across several different surgical techniques including retropubic suspensions (4,5), pubovaginal slings (PVS) (6,7), and tension free procedures (8). Currently, it is not fully known if pre-operative urodynamic data can be used to stratify surgical risk for MUI patients undergoing incontinence surgery. Consequently, our purpose was to determine if women with clinically diagnosed mixed urinary incontinence (MUI) and urodynamic detrusor overactivity have less improvement in urinary symptoms after pubovaginal sling surgery (PVS), compared to MUI without urodynamic detrusor overactivity.

MATERIALS AND METHODS

Women treated with pubovaginal slings between June 1998 and April 2005 were retrospectively identified from surgical case logs. For this study, the International Continence Society (ICS) definition of MUI was used, as cited above. For data extraction purposes, the definition was contracted to a documented clinical history of both stress and urge incontinence symptoms occurring more than once a week. For patients meeting these criteria, charts were reviewed for demographic, physical exam, urodynamic, surgical, and post operative data.

Prior to surgery, all patients had been evaluated with a Laborie Aquarius (Williston, VT) multichannel urodynamic system synchronized with fluoroscopic imaging. Studies were performed using International Continence Society good urodynamic technique recommendations. All patients had been screened for unrecognized urinary tract infections prior to testing. Testing was performed in the standing/upright position with bladder/ rectal air charged catheters. The urodynamic protocol included standardized filling rates of 55 cc/minute with Renografin (Bracco Diagnostics Inc, Princeton NJ) until the feeling of strong urge, an uninhibited detrusor contraction causing incontinence, or a 400 cc limit. Valsalva leak point pressures were measured at least twice at volumes correlating to feelings of strong urge or 400 cc. If urge incontinence occurred prior to Valsalva testing, the detrusor pressures were allowed to nadir and the bladder was refilled to the highest previously recorded volume and Valsalva testing was performed. All pressure/flow studies utilized intubated flow rates. Fluoroscopic images in the anterior-posterior and lateral positions were taken regularly during the study and were correlated to the cystometrogram tracings. All studies were performed by an experienced urogynecology nurse trained in urodynamic testing.

Detrusor overactivity (DO) was defined as any 5 cm H_20 symptomatic involuntary rise in detrusor pressure during the testing, per ICS recommendations. For this study, no differentiation was made between spontaneous or provoked DO. The number of contractions and maximum contraction amplitude was not recorded. All detrusor overactivity was considered idiopathic unless a relevant neurologic condition was present. Based on these definitions, patients were divided into two groups, those with urodynamic proven detrusor overactivity (Group A) and those without overactivity (Group B).

All patients had been treated with a cadaveric dermis bladder neck sling (9) or autologous rectus fascia bladder neck sling suspended over the rectus fascia. Operative data, including operative time, blood loss, and complications, were recorded. Post operative retention, defined as clean intermittent catheterization post void residual greater than 150 cc, was documented. Post operative care followed a specific protocol including instructions for quantifying the number of incontinence pads used per day starting 72 hours prior to a scheduled follow up visit. All patients were scheduled for at least 3 routine follow up visits during the first 12 months after surgery and then at 6 to 12 month intervals afterwards. Incontinence pad type was not standardized in this retrospective study.

At each visit, both before and after PVS, a registered urogynecology nurse solicited information on patient's current pad usage and all patients completed a validated quality of life questionnaire, the Urogenital Distress Inventory 6 (UDI-6). This questionnaire is a robust 6 domain validated urinary incontinence specific questionnaire that measures distress caused by multiple urinary symptoms, including urgency, urge incontinence, stress incontinence, urinary retention, and pelvic pain (10).

End points used in this study included change in pad use/day and change in UDI scores after PVS surgery. The change in total UDI score after PVS and

change in pad use/day was calculated for each subject using data available from each patient's initial and last follow-up visit. Continuous variables were compared using Student-t-Tests or Wilcoxon sum rank tests. Binomial variables were compared with Chi-Square tests. Tests with $p < 0.05$ were considered statistically significant.

RESULTS

A total 262 patient underwent PVS between 1998 and 2005. Seventy-three met the inclusion criteria for pre-operative MUI prior to PVS. Cadaveric dermis was utilized in 70 patients and rectus fascia used in 3. Of the 73 patients, 31 had preoperative urodynamic overactivity (Group A), all of which were classified as idiopathic, and 42 did not have urodynamic overactivity (Group B). Two patients in Group A were treated with rectus fascia and 1 in Group B. One patient in Group B had an L5 radiculopathy, but demonstrated no urodynamic changes. Mean follow-up after PVS for Groups A and B were 16 and 15 months (range 1 - 24, $p = 0.59$).

Prior to PVS, 7 patients in Group A and 9 in Group B were taking anticholinergic medications. Four patients in Group A and 7 in Group B had previous urethral bulking agent treatment. Vaginal vault prolapse was a common comorbidity, although both groups showed similar degrees of prolapse along the anterior wall (2.7 vs. 2.5 Baden Walker Grade, $p = 0.56$), apical (1.0 vs. 1.2 BW, $p = 0.75$), and posterior wall (1.3 vs. 1.0 BW, $p = 0.47$). Pre-operative urodynamic characteristics were likewise similar, with comparable flow rates (20 and 23 mL/s, $p = 0.36$), Valsalva leak point pressures (60 and 74 cm H_20, $p = 0.160$), and post void residuals (13 and 31 mL, $p = 0.114$). After PVS, Groups A and B reported 2.5 and 5.2 days of urinary retention ($p = 0.0002$). There were no other significant differences between the two groups when comparing age, parity, menopause status, concomitant vaginal vault prolapse, or surgical blood loss, summarized in Table-1.

Groups A and B had similar pre-operative UDI scores (Figure-1). After PVS, mean changes in total UDI-6 scores were - 8.0 and - 10.2 ($p = 0.030$), respectively. The study was not adequately powered to perform a meaningful sub-group analysis of the UDI-6 domains. Prior to surgery, both groups also had similar pad use/day (Figure-2). After PVS mean change in pad use/day was - 2.57 and 2.49 ($p = 0.64$) for Groups A and B, respectively. After PVS, 21 (68%) and 28 (67%) patients in Group A and B, respectively, did not wear pads for protection ($p = 0.92$). A total of

Table 1 *– Patient demographics.*

		Group A (+ Overactivity)	**Group B** (- Overactivity)	**p Value**
Mean age		57.6 years (SD 12.6)	58.6 years (SD 12.1)	0.69
Mean parity		2.6 births (SD 1.7)	2.4 births (SD 1.6)	0.47
Hysterectomy	Yes	16 patients	16 patients	0.62
Prolapse	Yes	25 patients	35 patients	0.77
Menopause	Post	25 patients	35 patients	0.77
Pre op anticholinergic		7 patients	9 patients	0.90
Pre op VLPP		60 cm H_20 (SD 27)	74 cm H_20 (SD 39)	0.16
Pre op flow rate		20 cc/s (SD 12)	23 cc/s (SD 17)	0.36
Bladder capacity		330 cc (SD 93)	355 cc (SD 143)	0.40
Mean blood loss		213 cc (SD 142)	273 cc (SD 159)	0.10
Post op retention		2.5 days (SD 2.2)	5.2 days (SD 3.3)	0.0002

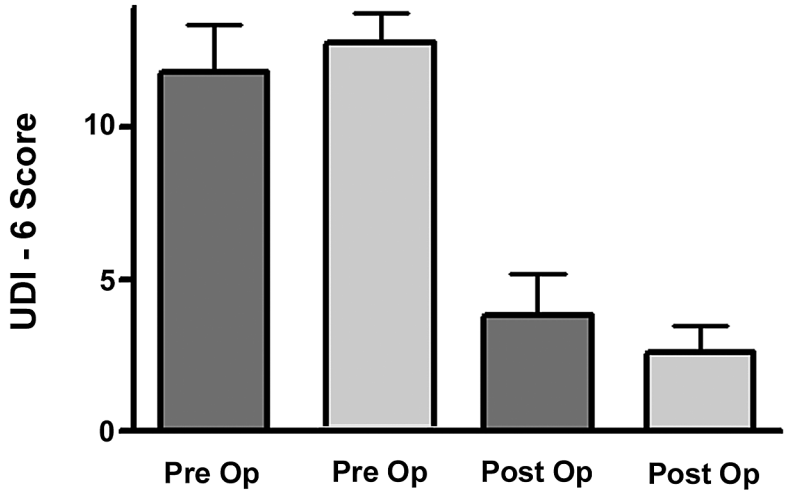

Figure 1 – *Mean UDI-6 scores before and after PVS. Group A = dark grey bars; Group B = light grey bars.*

6 patients, 3 within each group required either a collagen injection or sling revision for persistent stress incontinence. For the 16 patients using anticholingeric medication before surgery, all continued to use the medication after PVS. No new patients were using anticholinergics at the last post operative visit.

COMMENTS

Risk factors that influence surgical outcomes in the MUI population are not well described or understood. Our study investigated whether MUI patients with DO were at risk for worse outcomes

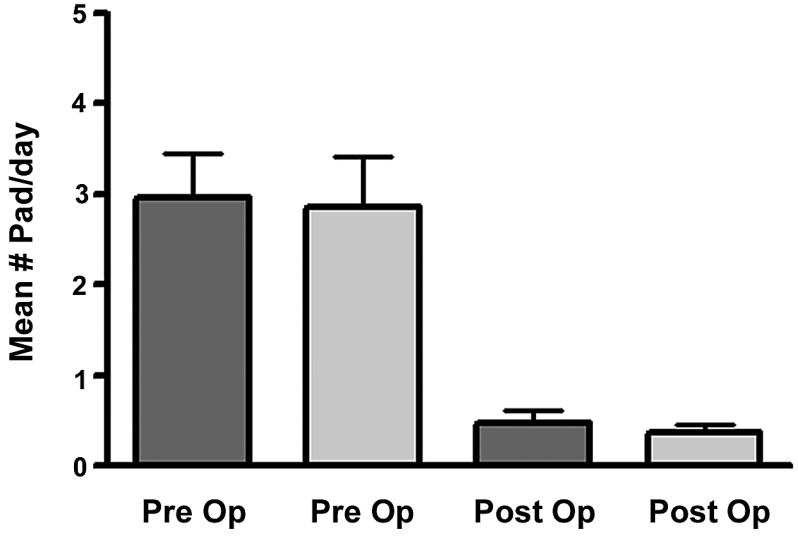

Figure 2 – *Mean pad use per day. Group A = dark grey bars; Group B = light grey bars.*

after PVS, compared to MUI patients without DO. We demonstrated that while both groups showed similar improvement in pad use/day, MUI patients with pre-operative DO had significantly less improvement in self reported urinary specific symptoms after PVS, as measured by the Urogenital Distress 6 quality of life questionnaire.

There is conflicting information regarding the impact of pre-operative urodynamic overactivity on surgical outcomes in the MUI populations. Kuzmarov studied 51 women with MUI prior to Marshall Marchetti Kranz (MMK) suspension and observed no relationship between detrusor overactivity and outcome (11). Del Campo Rodriguez found no difference in cure rates after Burch or MMK for 44 women with pre-existing urodynamic overactivity (12). Miller et al. also did not find an association between pre-operative detrusor overactivity and return of bladder function (13). However, Paick et al. recently reported that MUI patients with uninhibited detrusor contractions during cystometry should be considered a high risk group for surgical failure following tension-free vaginal tape, suprapubic arc sling, or transobturator tape treatments (14). Depending on the endpoints used, our study supports both sides of these contradictory series. In our study we noted no difference between groups using the endpoint pad usage/day but noted a significant different when comparing health related quality of life (HRQOL) scores. It is possible that our study was underpowered to detect a meaningful change between a weak variable, such as pad usage/day, but adequately powered to detect a difference when using a strong validated variable, such as the UDI-6 total score. Consequently, discrepancies in the literature regarding the relationships between MUI, DO, and surgical outcomes may be attributed to wide variation in study endpoints. More research with standardized endpoints is clearly needed in this area before these relationships can be better understood.

It is unlikely that patient demographics greatly influenced our findings. In general, our patient sample represented a typical MUI population seeking treatment. In our study of 73 women, preoperative DO was identified in 42%. These findings are similar to the 43% prevalence found in much a larger series of 1626 women with MUI (15). Furthermore, the Valsalva leak point pressures and prevalence of vaginal vault prolapse found within our patient sample are similar to other MUI surgical series (6,13-15). Within the study, women with and without DO also appeared to have similar demographics. Stress incontinence intensity may have been a confounding factor, although this is unlikely since groups had similar mean pre-operative UDI-6 scores and Valsalva leak points.

Likewise, it is unlikely that findings in this study can be attributed to the UDI-6 instrument. The UDI-6 QOL questionnaire used in this study is a well validated, sensitive, and specific urinary symptom specific instrument. The questionnaire has 6 domains, including urinary urgency, urge incontinence, stress incontinence, urinary retention, and pelvic pain and has been reliably validated across patient age and diagnosis. Although total UDI-6 score has not been routinely used to assess outcomes after MUI surgery, it is commonly used to determine outcomes for overactive bladder treatment (16) and effectiveness for other anti incontinence interventions (17). Future investigations with other validated quality of life (QOL) questionnaires should determine if the results generated by the UDI-6 in this study are questionnaire specific.

However, a limitation of this study is that MUI was considered a binomial variable and patients were stratified into those with DO (Group A) and those without (Group B). Since voiding diaries were not available, we did not sub-stratify Group A or Group B by number of urge incontinence episodes either before or after surgery. Given the small sample size, we also chose not to sub-stratify DO in Group A by number of contractions or amplitude of contraction. Consequently, it is possible that the intensity of urgency symptoms is a confounding factor in our findings. With a larger sample size, we may have confirmed Kulseng-Hanssen's recently published findings that MUI patients with urge predominant symptoms may experience a lower QOL after TVT, compared to MUI patients with stress predominant symptoms (18). A larger sample size may have better discerned the influence of symptom intensity on MUI surgical outcome.

A further limitation of this and of all urodynamic based MUI investigations is that urodynamic protocols vary widely from center to center. In 2003, Sriram et al. performed an audit of United Kingdom

urodynamic practitioners and found considerable disagreement among standardization of catheter zeroing techniques and application of urodynamic definitions (19). Verbal instructions given to patients during testing have also been shown influence the detection of idiopathic detrusor overactivity in patients with clinical symptoms of urinary urgency (20). Although we acknowledge the difficulty in reproducing urodynamic data, we attempted to minimize patient to patient variability by adhering to a written urodynamic protocol and having a single practitioner perform all studies. However, we do acknowledge inter-institutional protocol variability as a further potential confounding factor in this study.

Finally, we recognize the limitations surrounding the retrospective design of this study. Although our patient population represents an unselected group of women presenting for evaluation and treatment of mixed incontinence, unrealized confounding variables may bias our retrospective data extraction. A prospective, multi-center study would better minimize potential bias.

CONCLUSION

PVS for treatment of MUI is associated with an improvement in pad usage/day and UDI-6 total scores. However, MUI patients with DO have less improvement in UDI-6 scores after PVS, compared to MUI patients without DO. Preoperative urodynamic testing, in combination with HR-QOL questionnaire administration, should be considered as a pre-operative tool for addressing post operative QOL expectations after PVS for this patient population.

CONFLICT OF INTEREST

None declared.

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Accepted after revision:
July 28, 2008

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EDITORIAL COMMENT

This is a nice paper by Stoffel et al. looking at one of the most difficult group of women we consider doing the sling surgery on: women with mixed urinary incontinence (MUI) and urodynamic detrusor overactivity (DO). The authors reviewed 73 women with preoperative MUI symptoms prior to sling surgery. MUI patients with and without DO were divided into two groups and followed-up with a questionnaire and pad test after the sling surgery.

Of the 73 patients, 31 women had DO and 42 did not. After surgery, both groups reported similar mean reduction in pad/day usage but MUI women with DO had less improvement in validated incontinence questionnaire despite a similar reduction if pad use/day. The UDI-6 QOL questionnaire used in this study is a well validated, sensitive, and specific urinary symptom specific instrument. However, a limitation of this study is that MUI was considered a binomial variable and patients were stratified into those with DO and those without. Voiding diaries were not available so a key parameter of number of urges incontinence episodes either before or after surgery were not available.

There are good data in this paper as the authors correctly pointed out that the sling operation for MUI is associated with an improvement in pad usage/day and symptom index. However, MUI patients with DO have less improvement in UDI-6 scores compared to MUI patients without DO.

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International Braz J Urol Vol. 34 (6): 772-773, November - December, 2008

Childhood Renal Lymphangiectasia

To the Editor,

An asymptomatic 4 month-old white female had a 2 x 3 cm faint birthmark on her mid-thoracic back consistent with a cutaneous telangiectasia. MRI of the spine incidentally demonstrated an infiltrative right renal lesion. Ultrasound showed an infiltrative lesion in the enlarged right kidney and proximal ipsilateral ureter as well as heterogeneously increased renal cortical echogenicity. Abdominal CT scan revealed a hypodense lesion (Hounsfield units from 0 to +20) infiltrating the renal pelvis and parenchyma, circumscribing the right kidney and proximal ureter (Figure-1, A). Delayed contrast images showed compression of the ureterovesical junction with medial displacement of the right ureter (Figure-1, B). Abdominal MRI characterized the lesion as heterogenously hyperintense and hypointense on T2 and T1 weighted images, respectively (Figure-2). Right kidney differential function was 28% by MAG-3 renal scan. The infiltrative character of the lesion without significant enhancement is consistent with a renal lymphangiectasia. At 2.5 years of follow-up, she remains asymptomatic without radiological change.

Renal lymphangiectasia is a rare, benign condition characterized by developmental malformation of the perirenal lymphatic system. The lymphatic structures that surround the kidney fail to establish normal communication with the rest of the lymphatic system. The physiopathological process is ectasia of lymphatic vessels without obstruction (1,2). It can be focal, unilateral or bilateral and may be found in pediatric or adult patients. There are reports of familial predisposition (2). Like other lymphatic lesions, renal lymphangiectasia can appear suddenly, grow rapidly, cease growth abruptly, or even regress spontaneously. Signs and symptoms may vary from none to microscopic or macroscopic hematuria, proteinuria, flank pain, abdominal pain/distension, palpable abdominal

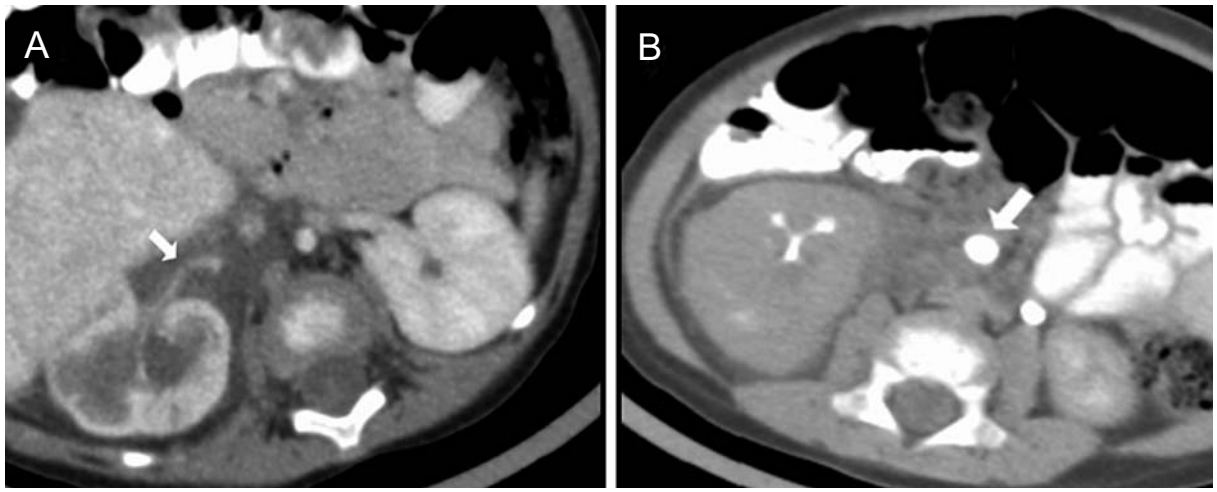

Figure 1 – *A) An infiltrative, hypodense lesion is identified in the renal sinus, parenchyma and perirenal space. The right renal artery is circumscribed by the lesion (arrow). B) Delayed CT image shows elongated and distorted collecting system by the renal sinus mass. The right ureter is enlarged and displaced medially (arrow).*

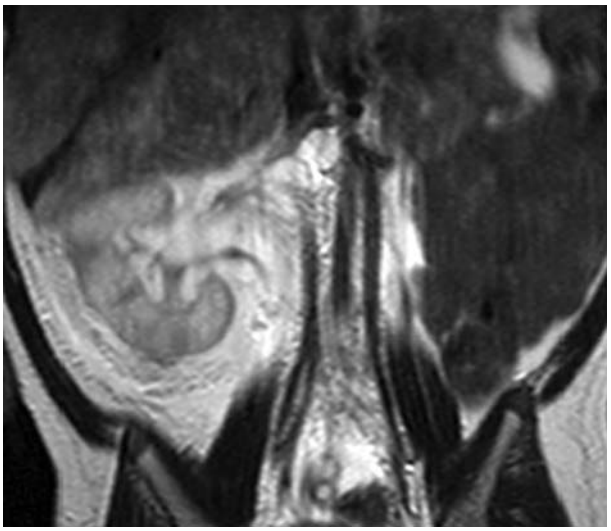

Figure 2 *– Coronal T2 weighted image shows the mass in the renal sinus and perirenal space. The fluid content of the lesion is inferred from T2 prolongation.*

mass, lower extremity edema and hypertension. Renal function is generally preserved.

Radiological imaging modalities have aided diagnosis, including renal US, IVP, CT, and MRI. Renal US can show an enlarged and lobulated kidney with increased echogenicity and loss of normal corticomedullary differentiation (2). The CT scan reveals multilocular cyst/fluid filled masses with thin walls in the perirenal and parapelvic region. The MRI can show hyperintensity of the renal parenchyma especially at the cortical region and hypointensity at the medullary region. Also, multiple hyperintense lesions in perirenal spaces on T2-weighted images can be appreciated. Pediatric differential diagnosis includes polycystic renal disease, urinoma, renal lymphoma with perirenal involvement, renal tumors, etc. The diagnosis can be confirmed by needle aspiration of chylous fluid or by renal biopsy but multi-modal imaging is characteristic.

Management is often conservative due to the benign behavior of the lesion. Percutaneous drainage with administration of intravenous albumin and enteral medium chain triglycerides may be indicated if symptoms or ascites develop. Several cases of cyst decortication have resulted in nephrectomy due to uncontrolled intraoperative bleeding. While some suggest that asymptomatic patients with unchanged cystic lesions on US do not require follow-up, we feel patients should undergo lifelong follow-up as occasionally renal function will deteriorate.

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International Braz J Urol
Vol. 34 (6):774-797, November - December, 2008

UROLOGICAL SURVEY

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STONE DISEASE

Plain radiography still is required in the planning of treatment for urolithiasis

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J Endourol. 2008; 22: 2201-5

Introduction: Nonenhanced computed tomography (NCT) is recognised as the most sensitive tool in diagnosis of renal tract calculi. However, its role as the sole imaging investigation, for decisions regarding management is less clear.
Objective: To determine the proportion of new stone patient referrals in which management is altered by interpretation of a plain abdominal kidneys, ureters and bladder (KUB) radiograph in addition to NCT.
Methods: One hundred consecutive new referrals to a national lithotripsy centre were considered prospectively for treatment of renal tract calculi.
Results: A significant change in management was undertaken in 17 patients on the basis of KUB findings. Eleven patients had radio-lucent ureteric stones, for which Extracorporeal Shockwave Lithotripsy (ESWL) was consequently not possible and who required endoscopic management. There were six inaccuracies in measurement of size or positioning on NCT. In a further 43 patients it was not possible to confirm management until the KUB was reviewed, although in these cases ESWL or expectant management was still pursued. Thus additional imaging with a KUB was required in order to confirm optimum management in 60 patients.
Conclusion: Additional plain radiography confers a significant advantage in the planning of treatment for urolithiasis once the diagnosis has been established by NCT because of information it provides regarding radiopacity as well as stone size and visibility. This information cannot be delivered by NCT alone. We therefore recommend that KUB imaging is performed on all new stone patients referred for treatment.

Editorial Comment

The study population is a select group - patients referred to a well-established national lithotripsy service in Scotland under well-established protocol and guidelines. The study may therefore underestimate the value of KUB - it is feasible that other patients evaluated at the point of entry (local urologist) may have undergone KUB imaging and a decision was made not to proceed with referral for SWL. In addition, the authors do not report the time interval between CT scan imaging at the local urologist office and subsequent KUB imaging at the tertiary referral center. It is possible that the impact reported for KUB was reflective of movement of the stone over time rather than added clarity from additional imaging.

The authors did not evaluate the utility of Hounsfield units to predict the radiolucent characteristic of the stone - it is possible that could negate the need for plain radiography. The authors did not have a PACS system that allowed them to directly measure stone size on the CT scan, nor did they have access to the full CT scan images - rather they relied on “select hard copies”. One would anticipate that the predictive value of CT scan imaging would increase were all the images available for review.

The authors note that renal pelvic and lower pole anatomy is helpful to predict shockwave success, however they do not report how this was interpreted on plain radiography. Coronal reconstructions of the NCCT may have provided useful information in this regard. The authors do not report the number of observers who measured the stones on radiographic imaging, nor do they comment on the inter-observer reliability of such measurements on CT and KUB.

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A comparison of the physical properties of four new generation flexible ureteroscopes: (de)flection, flow properties, torsion stiffness, and optical characteristics

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J Endourol. 2008; 22: 2227-34

Background and Purpose: Several kinds of flexible ureteroscopes are in use for the removal of kidney stones. This study evaluated and compared the characteristics of four new-generation flexible ureteroscopes.
Materials and Methods: The flexible ureteroscopes studied were: the ACMI Dur-8 Elite, the Storz Flex-X2 the Olympus XURF-P5, and the Wolf 7325.076. Measured properties included (de)flection, instrument insertion, flow properties, torsion stiffness, and optical characteristics. Active tip deflection and irrigation flow rates with and without various endoscopic tools were assessed.
Results: All ureteroscopes score better on (de)flection with an empty working channel, compared with a channel when tools are inserted (differences minimum 0.3 degrees--maximum 80.6 degrees). The Olympus XURF-P5 is the only ureteroscope with passive (de)flection capability, whereas the ACMI DUR-8 Elite is the only ureteroscope that has a secondary active (de)flection capability. The Storz Flex-X2 and the Wolf 7325.076 ureteroscopes show nearly identical best deflection capabilities with and without tools inserted in the working channel. The longest (Olympus XURF-P5, 70 cm) and shortest (ACMI DUR-8 Elite, 64 cm) ureteroscopes have, respectively, the lowest and highest flow rates. Best optical quality is offered by the Olympus XURF-P5 and Wolf 7325.076 ureteroscopes, which have low optical distortion (-9.7; -7.7%), high resolving power (17.95; 16.00 line pairs per millimeter), and a large field of view (62.9; 63.2 degrees). The Storz Flex-X2 and Wolf 7325.076 ureteroscopes have lowest torsion stiffness.
Conclusions: The ex vivo evaluation of the deflection capabilities, passage of instruments, flow properties, torsion stiffness, and optical characteristics yielded quantitative measures of the in vivo performance capabilities of four new-generation flexible ureteroscopes. New ureteroscopes should be subjected to this or similar evaluation and comparison. Only in this way can the urologist make an informed and objective decision regarding appropriate instrument choice.

Editorial Comment

In general, this is an elaborate and well-conducted study that offers helpful information in selecting the best flexible ureteroscope for clinical use. However, the study is significantly limited by the lack of statistical analysis. The authors do not report the visual acuity of the 4 observers who subjectively scored the "resolving power" of the ureteroscopes. Though the radius of curvature was qualitatively reported, no quantitative analysis was presented.

The limiting factor in endoscopy is the quality of image. Image is everything! One can conclude based on this study that the Wolf flexible ureteroscope is optimal - low optical distortion, high resolving power and large field of view, with superior illumination compared to the Olympus scope. One limitation of this study is that only one scope was tested from each manufacturer - variance may exist between multiple scopes of the same make and model.

Often image quality deteriorates quickly in the face of bleeding or stone fragmentation - it would be useful to evaluate the ureteroscopes under these conditions.

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ENDOUROLOGY & LAPAROSCOPY

Laparoscopic ureterolysis and omental wrapping

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Urology. 2008; 72: 853-8

Objectives: To describe our laparoscopic technique of ureterolysis and omental wrapping using the LigaSure device for the treatment of idiopathic retroperitoneal fibrosis.
Methods: Four bilateral laparoscopic ureterolyses (LUs) and two unilateral LUs were performed in 6 male patients (mean age 47 years). Of the 6 patients, 4 underwent LU without having undergone medical therapy before surgery and 2 underwent LU after medical therapy failure. All had had ureteral stents placed before surgery. The ureters were completely freed from the fibrotic tissue using an Overholt laparoscopic forceps and 10-mm LigaSure atlas. An omental wrap was passed behind the colonic flexure, placed around the ureter, and fixed to the psoas muscle.
Results: The mean operating time was 80 minutes (range 75 and 85) for the unilateral LUs and 200 minutes (range 180-225) for the bilateral procedures. The mean blood loss was 75 mL (range 50 and 100) during LUs and 150 mL (range 80-220) during bilateral LUs. The mean hospital stay was 3.33 days (range 2-5). All indwelling ureteral stents were removed at 4 weeks postoperatively. At a mean follow-up of 37.5 months (range 23-59), all patients were free of symptom and all renal units were unobstructed.
Conclusions: In our experience of LUs and omental wrapping, the reproduction of each step of open surgery seems to offer excellent midterm outcomes. The use of the LigaSure simplified the laparoscopic procedure and made it feasible and safe. We believe that the minimally invasive nature and high effectiveness of LU suggest consideration of this procedure as first-line treatment of idiopathic retroperitoneal fibrosis.

Editorial Comment

The management of retroperitoneal idiopathic fibrosis has evolved from complex open surgery to medical therapy with reasonable success rates and the more conservative management for unfit patients for surgery or patients that did not want to undergo through a long recovery with open surgery may simply have ureteral stents placed and changed them sporadically.

As in our experience, and the authors the Laparoscopic approach appears to be as effective as open surgery but medical therapy may offer a success rate of 50%-80%, with probably a lower effectiveness in patients with severe disease. Longer follow-up is necessary but this is another small series that laparoscopic approach may be as effective as open surgery.

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Artery-only occlusion may provide superior renal preservation during laparoscopic partial nephrectomy

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Urology. 2008; 72: 843-6

Objectives: Artery-only occlusion (AO) has been used during nephron-sparing surgery to reduce ischemic damage. However, this has not been demonstrated in laparoscopic partial nephrectomy (LPN). We compared our experience with AO and both artery and vein occlusion (AV) in LPN to optimize the method of ischemia.
Methods: This retrospective case-control study identified 25 patients who underwent AO during LPN and matched them to a cohort of 53 patients who underwent LPN with AV. The groups were compared for ischemia time, blood loss, transfusion rate, and renal function.
Results: The 2 cohorts were comparable on demographic data. Blood loss was similar, with AO and AV demonstrating equivalent transfusion rates. The 2 cohorts had similar warm ischemia times. Positive margin rate was not affected by venous backflow in the AO cohort (0% AO vs 1.9% AV, P = .679). No significant postoperative change in creatinine (Cr) or creatinine clearance (CrCl) was seen for AO; however, a significant change in Cr and CrCl was seen in AV.
Conclusions: AO during LPN does not lead to a greater blood loss or an increased warm ischemia time. The benefit of AO on renal function is significant and requires further investigation.

Editorial Comment

Laparoscopic partial nephrectomy has evolved due to better laparoscopic instruments, high volume surgeons and institutions. Renal warm-Ischemia reperfusion injury remains a very controversial and complex issue without many answers. From optimal ischemia time to ameliorate injury to ideal temperature for renal cooling to preserve renal function are still big question marks. The idea of arterial clamping only allowing venous back flow leakage may cause less visualization and more bleeding but protective mechanism for warm-Ischemia reperfusion injury may be related to the possibility of leakage of adhesion molecules or oxygen radical scavengers that may cause protection but these issues need future investigation.

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IMAGING

Utility of PET/CT in differentiating benign from malignant adrenal nodules in patients with cancer

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AJR Am J Roentgenol. 2008; 191: 1545-51

Objective: The purpose of this retrospective study was to determine the sensitivity and specificity of combined PET/CT in differentiating benign from malignant adrenal nodules measuring at least 1 cm in diameter in patients with cancer.

Materials and Methods: We reviewed the radiology reports and images of patients with known malignant disease who had undergone PET/CT for cancer staging or surveillance and who had adrenal nodules at least 1 cm in diameter. We identified 112 adrenal nodules in 96 patients. Two-dimensional PET had been performed 1 hour after administration of (18)F-FDG. Unenhanced CT was performed for attenuation correction, to determine lesion size, and for coregistration with PET data. Adrenal nodules were considered to have a positive PET result if the average standardized uptake value was greater than that of the liver. Follow-up data and biopsy reports were used to determine the pathologic status of the adrenal nodules.
Results: Thirty adrenal lesions were malignant. Twenty-five of the 30 malignant nodules had positive PET results. Twelve of 82 benign nodules were PET positive with a sensitivity of 83.3% and specificity of 85.4%. Patients with four of five malignant nodules with negative PET results had received previous therapy. The positive predictive value for detection of malignant lesions was 67%, and the negative predictive value was 93%.
Conclusion: Adrenal masses that are not FDG avid are likely to be benign with a high negative predictive value. Especially in patients undergoing therapy, however, there is a small but statistically significant false-negative rate. A considerable proportion of benign nodules have increased FDG activity.

Editorial Comment

Accurate characterization of most adrenal lesions is usually obtained with either CT or MRI. The use of standard CT techniques (unenhanced CT attenuation and CT washouts-absolute percentage) isolated or combined with MRI techniques ("chemical shift imaging", diffusion-weighted images and 3D-spectroscopy) are usually sufficient for the differentiation between benign and malignant lesion in the vast majority of adrenal nodules. Nuclear medicine studies prove to be useful adjuncts. Controversial reports have been published on the role of PET/CT in this clinical and radiologic setting because some adrenal adenomas and inflammatory / infectious lesions demonstrate slight increased radiotracer uptake. Similarly, necrotic or hemorrhagic malignant adrenal lesions occasionally may cause false-negative results.

The authors of this manuscript show that although with these few limitations PET/CT is useful for characterizing adrenal nodules. In our opinion, PET/CT should be used whenever CT and / or MRI techniques are not diagnostic. One important point to consider is that all these imaging techniques are complimentary and thus can be associated since they use fundamentally different biologic principles. Following this simplified algorithm, the use of image-guided adrenal biopsy will be in the near future used only in those rare patients where adrenal lesions remain indeterminate after CT, MRI and PET/CT techniques.

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Follow-up after percutaneous radiofrequency ablation of renal cell carcinoma: contrast-enhanced sonography versus contrast-enhanced CT or MRI

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Objective: The purpose of this study was to assess, with contrast-enhanced CT or MRI as the reference imaging technique, the diagnostic performance of low-mechanical-index contrast-enhanced sonography in detecting local tumor progression after percutaneous radiofrequency ablation of renal tumors.

Materials and Methods: Twenty-nine patients with 30 renal tumors (18 men, 11 women; mean age, 73 years; range, 53-83 years) underwent percutaneous radiofrequency ablation at a single center between March 1998 and January 2007. The imaging follow-up schedule was both contrast-enhanced sonography and CT or MRI 4 months after completion of treatment and every 4 months for the first year. Thereafter, the follow-up schedule was contrast-enhanced sonography every 4 months with CT or MRI every 8 months. The chi-square test with Yates correction was used to evaluate positive and negative predictive values and accuracy.
Results: One patient was scheduled to undergo surgical resection, and another patient was lost to follow-up. Twenty-seven patients with 28 renal tumors participated in follow-up. The concordance between contrast-enhanced sonographic and CT or MRI findings was 100% for 27 of 28 tumors (96.4%) that had a hypervascular pattern before treatment. In the case of the tumor that was hypovascular at imaging performed before percutaneous radiofrequency ablation, local tumor progression was missed at contrast-enhanced sonography. The sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy of contrast-enhanced sonography were 96.6%, 100%, 100%, 95.8%, and 98.1%.
Conclusion: Contrast-enhanced sonography is an effective alternative to CT and MRI in the follow-up of renal tumors managed with percutaneous radiofrequency ablation.

Editorial Comment

Percutaneous radiofrequency (RF) ablation and cryoablation are increasingly being used as minimally invasive treatments for renal tumors in patients whose condition is inadequate for surgery. Accurate imaging evaluation of ablated tumors is essential in order to detect the adequacy of treatment and to guide patient management. In comparison with normal renal parenchyma, renal tumors treated with RF ablation usually appear as low-attenuation regions at computed tomography (CT). On conventional magnetic resonance imaging (MRI) these treated lesions appears as areas with iso- to hyperintensity at T1-weighted imaging and area of hypointensity at T2-weighted imaging. After intravenous injection of contrast material, successfully treated renal tumors appear in either one method, as focal masses that demonstrate no evidence of contrast enhancement. These focal masses continue to decrease in size during the follow-up examinations. Residual or recurrent tumor is characterized by the presence of abnormal areas of contrast enhancement.

The authors of this manuscript compared the findings at real-time low-mechanical-index contrast-enhanced sonography with those at CT or MRI in the follow-up of patients with renal cell carcinoma treated with RF ablation. They showed that in patients presenting hypervascular tumors before treatment, contrast-enhanced sonography has similar accuracy to that of CT or MRI for the detection of local tumor progression. Hypovascular renal tumors however were not adequately assessed by this technique. Since the evaluation of perfusion patterns with contrast-enhanced ultrasonography using contrast-pulse sequence imaging is useful in the follow-up of cryoablated renal tumors, it seems that this method is an effective alternative to CT and MRI in the follow-up of renal tumors in patients in whom the use of iodinated or paramagnetic contrast agent should be avoided and in those with any other clinical condition that precludes the use of CT or MRI evaluation.

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UROGENITAL TRAUMA

American Association for the Surgery of Trauma Organ Injury Scale I: spleen, liver, and kidney, validation based on the National Trauma Data Bank

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J Am Coll Surg. 2008; 207: 646-55

Background: This study attempts to validate the American Association for the Surgery of Trauma (AAST) Organ Injury Scale (OIS) for spleen, liver, and kidney injuries using the National Trauma Data Bank (NTDB).
Study Design: All NTDB entries with Abbreviated Injury Scale codes for spleen, liver, and kidney were classified by OIS grade. Injuries were stratified either as an isolated intraabdominal organ injury or in combination with other abdominal injuries. Isolated abdominal solid organ injuries were additionally stratified by presence of severe head injury and survival past 24 hours. The patients in each grading category were analyzed for mortality, operative rate, hospital length of stay, ICU length of stay, and charges incurred.
Results: There were 54,148 NTDB entries (2.7%) with Abbreviated Injury Scale-coded injuries to the spleen, liver, or kidney. In 35,897, this was an isolated abdominal solid organ injury. For patients in which the solid organ in question was not the sole abdominal injury, a statistically significant increase ($p < or = 0.05$) in mortality, organ-specific operative rate, and hospital charges was associated with increasing OIS grade; the exception was grade VI hepatic injuries. Hospital and ICU lengths of stay did not show substantial increase with increasing OIS grade. When isolated organ injuries were examined, there were statistically significant increases ($p < or = 0.05$) in all outcomes variables corresponding with increasing OIS grade. Severe head injury appears to influence mortality, but none of the other outcomes variables. Patients with other intraabdominal injuries had comparable quantitative outcomes results with the isolated abdominal organ injury groups for all OIS grades.
Conclusions: This study validates and quantifies outcomes reflective of increasing injury severity associated with increasing OIS grades for specific solid organ injuries alone, and in combination with other abdominal injuries.

Editorial Comment

The original AAST classification schema for traumatic renal injuries was published back in 1989 in the Journal of Trauma.(1) The sub-classification of the injuries into grades I - IV were mostly based on expert opinion and poorly constructed retrospective analyses. Despite such poor Oxford Level of Evidence of support for the classification schema, it has stood the test of time. The above paper by Tinkoff et al. is based on Nation Trauma Data Bank (NTDB) V.5.0 and Kuan et al. (2) based on NTBD V.4.0 came to the same conclusions as the reproducible validity of the scaling. The strength of the NTDB is that it is a large repository of trauma data from 405 trauma centers from across the US. Such pooling of data results in large numbers and the power to make statistically significant conclusions. As the standard of care for blunt Grade 1-IV renal injuries is nonoperative and isolated low grade penetrating injuries also trending to nonoperative, it is not surprising that NTDB data shows that 90. 9 % of all renal injuries can be safely managed non-operatively. Furthermore, patients with isolated kidney injuries, where severe traumatic brain injuries and deaths < 24 hours from arrival at the ED were excluded from study showed an incremental and statistically significant increase across all parameters from Grade I and II to Grade V - such as in mortality (1.5% to 10.7%), surgical exploration (4% to 73.3%), length of hospitalization (8.0 to 16.8 days) to ICU days (3.2 to 8.5 days). Another interesting finding was the economics of solid organ injuries. Hospital charges for solid organ injury were remarkably similar for liver, spleen and kidney. Average overall hospital charges are $72, 263 - $75,781. With isolated kidney injuries, the charges were about $6000 per day.

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Analysis of urologic complications after radical hysterectomy

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Objective: Injuries of the ureter or bladder or development of vesicovaginal and ureterovaginal fistulas are the most serious complications in gynecological surgery.
Study Design: This study included 536 women who underwent radical hysterectomy because of invasive cancer of the cervix uteri.
Results: During the surgery the ureter was injured in 1.32% of cases, whereas the percentage of bladder injuries was 1.49. In the early postoperative period vesicovaginal or ureterovaginal fistulas appeared in 2.61% and 2.43% of cases, respectively.
Conclusion: The stage of the disease, obesity, diabetes, and postoperative surgical infection acted as predisposing factors of the urinary tract complications.

Editorial Comment

Lower urinary tract injury during gynecologic surgery is relatively uncommon. Bladder injuries are the predominant iatrogenic urologic injury. Bladder injuries are usually recognized and repaired immediately, and potential complications are typically minor. Ureteral injuries, however, are typically recognized in a delayed fashion and have the potential to be life threatening, or result in permanent kidney damage or nephrectomy.

Iatrogenic ureteral injuries are a potential complication of any open or endoscopic pelvic operation. Gynecologic surgery accounts for roughly 75% of all iatrogenic ureteral injuries, with the remaining occurring during colorectal, general, vascular, and urologic surgery. The ureter is injured in roughly 0.5-2% of all hysterectomies and routine gynecologic pelvic operations and in about 2-10% of all radical hysterectomies. Likic et al. report a lower rate of ureteral injury of only 1.32%, but this reported decline over the years is due to improved patient selection, surgery limitation to mostly low-stage disease, decreased use of preoperative radiation, and modifications in surgical technique that limit extreme skeletonization of the ureter. Of iatrogenic ureteral injuries from gynecologic surgery, roughly 50% are from radical hysterectomy, 40% from abdominal hysterectomy, and < 5% from vaginal hysterectomy. All gynecologic ureteral injuries occur to the distal third of the ureter. Ureteral injuries during laparoscopic gynecologic surgeries typically occur during laser ablative endometriosis surgery or laparoscopic assisted vaginal hysterectomy. In gynecologic surgery, bladder injury most commonly occurs during abdominal hysterectomy. The bladder can be injured at four specific sites, on incising the parietal peritoneum, entering the vesicouterine fold, separating the bladder from the uterine fundus,

cervix, or upper vagina, entering the anterior vagina, or on mobilizing or suturing the vaginal vault. If a bladder injury is noted at this time, it can usually be easily managed by a 2 or 3 layer closure. Retrograde bladder filling with blue colored saline facilitates bladder injury diagnosis. Undiagnosed intraoperative injuries to the bladder typically present days to weeks after surgery. In patients with prior pelvic irradiation, fistulas can present months to even years after hysterectomy.

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PATHOLOGY

Renal cell carcinomas with papillary architecture and clear cell components: the utility of immunohistochemical and cytogenetical analyses in differential diagnosis

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Although histologic features enable an accurate diagnosis in most renal carcinomas, overlapping morphologic findings between some renal neoplasms make subclassification difficult. Some renal carcinomas show papillary architecture but are composed extensively of cells with clear cytoplasm, and it is unclear whether they should be classified as clear cell renal cell carcinomas or papillary renal cell carcinomas. We analyzed the immunohistochemical profiles and the cytogenetic patterns of 14 renal carcinomas showing papillary architecture in which there were variable amounts of cells with clear cytoplasm. The patients were 8 women and 6 men (mean age: 54 y). Immunohistochemistry and fluorescence in situ hybridization analysis distinguished 2 different groups. The first consisted of 10 renal cell carcinomas with strong immunoreactivity for alpha-methyl coenzyme A racemase, of which 9 also expressed cytokeratin 7. All of these neoplasms showed gains of chromosome 7 or 17 and chromosome Y was lost in all the male patients whereas 3p deletion was detected only in one case. In the other 4 renal cell carcinomas, cytokeratin 7 was not detected and alpha-methylacyl-CoA racemase was positive in only 1. In these neoplasms, no gain of chromosome 7 or 17 and no loss of chromosome Y were observed, whereas 3p deletion was detected in 3 of them. None of the 14 neoplasms showed immunoreactivity for TFE3. The combined use of immunohistochemistry and cytogenetics enabled us to provide a definitive diagnosis for 12 of 14 renal cell carcinomas with papillary architecture and clear cell components: 9 cases were confirmed to be papillary renal cell carcinomas and 3 cases were confirmed to be clear cell renal cell carcinomas. Despite these ancillary techniques, 2 cases remained unclassified. Our study establishes the utility of these procedures in accurately classifying the great majority of renal cell carcinomas with these findings.

Editorial Comment

In some tumors, the pathologist finds clear cell component in an otherwise papillary tumor. The usual papillary renal cell carcinoma may be either type I or II. In the former, the cells have scant cytoplasm and due

to this cytological feature, the tumor has a blue tinge in the microscopic examination. Type II tumors have abundant eosinophilic cytoplasm. In case there is a clear cell component, the differential diagnosis is papillary renal cell carcinoma with clear cell component vs. clear cell (conventional) renal cell carcinoma with papillary features. The study by Gobbo et al. shows that immunohistochemical and cytogenetical analyses are important for the differential diagnosis.

Two other tumors that may have papillary architecture with clear cell component must be recognized: the renal carcinoma associated with Xp11.2 translocations/TFE3 gene fusions (1) and the renal cell carcinoma associated with acquired cystic kidney disease (2). The latter is easily diagnosed due to the association with patients submitted to hemodialysis. To exclude the former it is necessary that TFE3 is negative in immunohistochemistry.

It is controversial the significance of a clear cell component when the diagnosis is the usual papillary renal cell carcinoma. Some consider these tumors to have a good prognosis, which goes along with their low nuclear grade. Others, however, have shown that a clear cell component is associated with a higher stage (3-5).

In spite of this controversy, it is important that the practicing pathologist adds to his pathology report the finding of a clear cell component in cases of usual papillary renal cell carcinoma.

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The role of pathologic prognostic factors in squamous cell carcinoma of the penis

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Purpose: The aim of this review was to identify prognostic pathologic factors which are independent from other clinical or molecular variables.
Methods: We reviewed the literature on morphological prognostic factors emphasizing our personal experience.

Results: We found that for a proper evaluation of prognostic factors a familiarity with penile complex anatomy is required. A biopsy of the primary tumor is not useful for a complete evaluation of prognostic factors other than malignancy and a resected specimen should be utilized. Penile carcinomas have a fairly predictable pattern of local, regional and systemic spread. Pathologic factors affecting patients outcome are multiple but it is difficult from the available studies using heterogeneous pathologic methodologies, different therapeutic approaches and ecologically variable patient populations to ascertain the independent validity of these factors. Invasion of perineural spaces by tumor, lymphatic-venous embolization and histological grade appear to be the most important pathologic predictors of nodal spread and cancer mortality. Other commonly cited factors influencing prognosis are tumor depth or thickness, anatomical site and size of the primary tumor, patterns of growth, irregular front of invasion, pathologic subtypes of the SCC, positive margins of resection and urethral invasion. A combination of two factors, histological grade and depth has been reported as significant predictor of cancer regional spread. After a preselection of significant factors, nomograms have been constructed to collectively evaluate the predictive power of various clinical and pathological indicators.
Conclusions: Among various factors perineurial invasion, vascular invasion and high histological grade appear to be the most important adverse pathological prognostic factors.

Editorial Comment

This is a very comprehensive review on a tumor that is very important in Brazil. A very recent article in Int Braz J Urol has shown the epidemiologic characteristics of penile cancer in this country (1). It is a very frequent tumor, predominantly affecting low income, non-neonatal circumcised males, Caucasian patients living in North and Northeast regions of Brazil where there may be a delay in obtaining specialized medical assistance.

Dr. Cubilla is an expert on penile carcinoma living in a country (Paraguay) also with a very high frequency of this tumor. He reviews the prognostic factors in squamous cell carcinoma. Among various factors, perineural invasion, vascular invasion and high histological grade appear to be the most important adverse pathological prognostic factors and should be reported by the pathologist. He also emphasizes the importance of the gross examination of the surgical specimen.

The grading of squamous cell carcinoma of the penis is based on the production of keratin. Abundant keratin production characterizes well differentiated tumors; keratinization of isolated cells moderately differentiated tumors; and, no production of keratin undifferentiated tumors.

The histopathologic subtypes are also important in prognosis. Verrucous carcinoma is a very well differentiated variant, the base is broad in all cases with pushing, regular borders composed of broad bulbous projections, which are usually restricted to the lamina propria but may extend deeper. They are slowly growing, locally infiltrative but do not metastasize. In some reports in the literature, this tumor is erroneously called giant condyloma. Verrucous carcinomas lack the HPV-related cellular changes characteristically seen in giant condyloma, and are not causally related to HPV, unlike giant condyloma (2).

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INVESTIGATIVE UROLOGY

Role of papaverine hydrochloride administration in patients with intractable renal colic: randomized prospective trial.

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Urology. 2008; 72: 987-90.

Objectives: To evaluate the therapeutic effect of papaverine hydrochloride in the treatment of patients with renal colic pain unresponsive to conventional treatment.
Methods: From March 2007 to January 2008, a total of 561 patients with severe renal colic pain due to a ureteral stone were treated with conventional agents (hyoscine-N-butylbromide and diclofenac sodium) in the emergency and urology departments. Of these 561 patients, 110, with no response to the treatment and persistent severe pain, were randomized into 3 groups for additional treatment. The patients in group 1 (n = 37) received intravenous hyoscine-N-butylbromide, those in group 2 (n = 37) received papaverine hydrochloride, and those in group 3 (n = 36) received pethidine. Before and after treatment, all patients completed a visual analog scale (VAS) questionnaire, with a scale of 0 (no pain) to 10 (maximal complaint), to measure their subjective pain. The mean VAS score of each group was compared with that of the other groups.
Results: The pretreatment mean VAS scores of all 3 groups were not significantly different statistically from each other (4.02 +/- 1.20, 4.36 +/- 1.97, and 4.27 +/- 1.50; P > .05). However, after treatment, the mean VAS scores of the patients treated with papaverine (0.93 +/- 0.29) and pethidine (0.81 +/- 0.38) were significantly different from those of the hycosine group (3.67 +/- 2.21; P < .001). However, the mean VAS scores of groups 2 and 3 were comparable (P = .67). Unlike opioids, no papaverine-related severe side effects were observed.
Conclusions: Our results indicate that papaverine hydrochloride can used in an effective manner in the management of renal colic pain in patients unresponsive to commonly used conventional agents.

Editorial Comment

Out of 561 patients with severe renal colic due to ureteral stone treated with hyoscine-N-butylbromide and diclofenac sodium, 110 who did not responded to the treatment were randomized into 3 groups for additional treatment.

The treatment protocol for these 3 groups consisted of a second repeat dose of intravenous hyoscine-N-butylbromide (20 mg in 250 mL 0.9% physiologic saline) administered within 20 minutes to group 1 (n _ 37); papaverine HCl (60 mg in 250 mL 0.9% physiological saline) administered intravenously within 20 minutes to group 2 (n _ 37); and pethidine (50 mg in 250 mL 0.9% physiologic saline) administered intravenously within 20 minutes to group 3 (n _36). No general side effects associated with hyoscine-Nbutylbromide or papaverine HCl administration was noted. However, a mild degree of bradycardia and hypotension occurred in 2 patients (5.5%) in the pethidine group, as well as mild to moderate degree of sedation in 13 patients (36%). The authors found that the severity of the pain was significantly diminished in the papaverine and pethidine groups (without significant difference between then).

The authors speculated that smooth muscle relaxation could be accepted as the main factor for papaverine action; nevertheless, the exact underlying mechanism of action could not be derived from the present study. The authors also proposed that possible changes caused by decreased renal output following the renovascular hemodynamic changes could also be responsible for this clinical effect.

It was concluded that although the classic and established conventional management of renal colic pain is highly effective, before second line opioid application, papaverine administration might be a valuable alternative for these patients.

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An in vitro study on human ureteric smooth muscle with the alpha1-adrenoceptor subtype blocker, tamsulosin.

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Objective: To study the effects of tamsulosin on ureteric contractions and its effects on the basal tone of human ureteric specimens, as clinical trials with tamsulosin have shown promising results in the spontaneous expulsion of lower ureteric calculus, but the mechanism of action of tamsulosin in the expulsion of ureteric calculus has not been elucidated in in-vitro studies on human ureters.
Materials and Methods: Human mid-ureteric specimens were obtained from live kidney donors. The specimen was transported in Krebs' solution and the isometric contraction of human ureteric smooth muscle was recorded in the presence of tamsulosin. Ureteric rings from 19 kidney donors were studied.
Results: At 100 microm tamsulosin the frequency of ureteric contraction was blocked completely, or the contraction frequency was reduced in 89% of specimens. There was no change in the frequency or in the amplitude of contraction in the remaining specimens. The basal tone of the ureter was reduced in 16% of the specimens.
Conclusion: Our results suggest that peristaltic activity in human ureteric smooth muscle is inhibited by tamsulosin. The effect of tamsulosin on basal tone is marginal.

Editorial Comment

Previous studies hypothesized that tamsulosin relaxes the ureteric smooth muscle, thereby facilitating the spontaneous passage of stone. Clinical studies demonstrated that tamsulosin decrease the colic pain and the number of colic episodes. Nevertheless, the exact mechanism of action is still controversial. The authors found that tamsulosin decreased or completely blocked the peristaltic contractions in 17 of 19 ureteric specimens studied in vitro. However, tamsulosin did not produce a decrease in baseline tension in 16 of 19 specimens. The results of this work support that the mechanism of action of tamsulosin is the inhibition of peristaltic contractions, and do not support the hypothesis that it causes a relaxation of ureteric smooth muscle.

In conclusion, the present study elegantly demonstrates that peristalsis in human ureter is inhibited by tamsulosin.

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RECONSTRUCTIVE UROLOGY

Surgical complications following radical cystectomy and orthotopic neobladders in women

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Purpose: Orthotopic neobladders have become the standard of care after radical cystectomy in select women with bladder cancer. We report early and late complications in 192 patients. Although medical complications were important, they were not the focus of this study.
Materials and Methods: Between January 1995 and December 2003, 192 women with a mean age of 50.6 years received an orthotopic neobladder after radical cystectomy for bladder cancer. Standard radical cystectomy was done. Ileal reservoirs were used, mostly in the form of an ileal W-neobladder. We evaluated the patients for functional outcome, early and late complications, and treatment for these complications.
Results: Two patients (1%) died of pulmonary embolism 1 to 2 weeks after cystectomy. Followup was 6 to 125 months (mean 54). Early complications included hemorrhage requiring reexploration in 1 case, postoperative blood transfusion in 1, wound infection in 8, prolonged ileus in 5, deep vein thrombosis in 5, pouch-vaginal fistula in 6, prolonged urinary leakage in 3, pouch-cutaneous fistula in 1 and early ureteral obstruction in 1. Of the 177 patients eligible for functional evaluation 62 experienced a total of 75 late complications, including stone disease in 18, ureteroileal stricture in 19, reflux in 22, intestinal obstruction in 2, incisional hernia in 2 and chronic pyelonephritis in 12. Early and late complications were treated accordingly with good outcomes.
Conclusions: Early and late complications develop in a significant number of patients. Most early complications may be treated conservatively, while late complications are mostly treated with endourological and/or open surgery. Close lifelong surveillance of patients is mandatory to detect and properly treat these complications.

Editorial Comment

Bladder cancer and its treatment with the specific anatomical aspect became a growing issue for women in recent years (1). The ileum conduit and the continent cutaneous pouch seemed to be the only option for female patients; whereas the ileum orthotopic neobladder was already the common surgical treatment for males. In the female, the different anatomical continence mechanism within the muscular pelvis had to be considered. A solution came from one of the centers with a high cystectomy frequency for both sexes where the orthotopic neobladder was performed in the early phase (2).

Ali-El-Dein B et al. (3) published the short and long-term follow-up of 192 women who received a orthotopic ileum neobladder during the time period 1995 - 2003. The complications were primarily noted in the upper urinary tract and mostly caused by implantation strictures within the first two years after the surgery. The complications experienced are similar to others, independent to the sex. As recently noted by the Consensus Conference on Bladder Cancer of the World Health Organization (WHO), this issue cannot be solved by a single suggestion (4).

Increased knowledge of the pelvic anatomy helped to reduce, as the authors stated, the frequency of neobladder-vaginal fistula described by Stenzl (5). Although the presented data includes those with the technique of orthotopic neobladder of an early period, the continence rate is similar to others (6).

The growing anatomical knowledge results in better intraoperative identification and preservation of the sphincteric area and neurovascular structures thus improving the long-term outcome and satisfaction (7).

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Apoptosis and effects of intracavernous bone marrow cell injection in a rat model of postprostatectomy erectile dysfunction

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Objectives: To investigate the pathophysiology of postprostatectomy erectile dysfunction (pPED) in a rat model of bilateral cavernous nerve ablation (BCNA) and to assess the effects of local bone marrow mononuclear cell (BMMNC) injection on erectile dysfunction (ED) and cavernosal cellular abnormalities caused by BCNA.
Design, Setting, and Participants: This was an experimental study in Fisher rats with BCNA.
Intervention: Intervention included BNCA, electrical stimulation of the pelvic ganglion, and local BMMNC injection.
Measurements: Erectile responses to electric pelvic ganglion stimulation were studied. Cavernous tissue was examined to determine the cell types undergoing apoptosis and to detect changes in protein and gene expression of neuronal nitric oxide synthase (nNOS) and endothelial nitric oxide synthase (eNOS) using real-time quantitative polymerase chain reaction (RTQ-PCR) and Western blotting. The effects of local BMMNC injection on these parameters were studied.
Results and Limitations: Diffuse apoptosis was noted in the connective tissue mesenchymal cells and vascular smooth muscle and endothelial cells. Compared with sham-operated controls, nNOS and eNOS levels were decreased after 3 wk and were normal (eNOS) or increased (nNOS) after 5 wk, suggesting spontaneous nerve regeneration. Despite nNOS recovery, erectile responses to electrical stimulation remained impaired after 5 wk, when mesenchymal cell apoptosis was the main persistent biologic abnormality. BMMNC injection decreased apoptotic cell numbers, accelerated the normalisation of nNOS and eNOS, and partially restored erectile responses at week 5.
Conclusions: Massive cell apoptosis may play a key role in the pathophysiology of pPED. In this animal model, apoptosis persisted despite spontaneous nerve regeneration, suggesting that the course of BCNA-induced cell

dysfunction was independent of reinnervation. BMMNC improved erectile function by inhibiting apoptosis and may hold promise for repairing penile cell damage caused by radical prostatectomy (RP).

Editorial Comment

Erectile dysfunction, which is a result of apoptosis caused by bilateral cavernous nerve ablation, is probably a "worst case scenario" after a radical prostatectomy (1). Even though human nerves cover the prostate surface similar to a net, post-operative erectile dysfunction can occur after an intended nerve sparing (2). The function of this net-like distribution was intraoperatively verified by Kaiho et al. (3). Although impotence following radical prostatectomy is multi-factorial, neurogenic factors also seem to play a major role. The most important prognostic factors for sexual potency recovery after radical prostatectomy are the number of spared nerve fibers, age, and sexual activity prior the surgery.

Fall and colleagues found in their rat model that bilateral cavernous nerve ablation causes apoptosis predominately in the vimentin +/ α-actin cells and is present throughout the cavernosal bodies, similar to the smooth muscle and the endothelial cells of the cavernosal arteries. With the intracavernosal delivery of bone-marrow mononucleated cells, apoptotic cells will be replaced to recover erectile function (1). This treatment strategy may constitute a promising alternative or complement treatments aimed at stimulating nerve regeneration similar to the recently reported testis stem cells that were differentiated into cells of all three germ layers (4).

The findings to protect corporal function noted by Fall et al. are not only relevant as a possible treatment immediately after radical prostatectomy, but also may be important for the aging but still sexually active patient. The improved knowledge of the nerve concourses will help to protect function [Sievert et al. Urology 2009, accepted for publication; scheduled for publication in March 2009] which might additionally minimize the erectile dysfunction with intracorporal injected bone-marrow mononucleated cells (2).

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UROLOGICAL ONCOLOGY

The natural history of noncastrate metastatic prostate cancer after radical prostatectomy

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Objectives: To characterise the natural history of metastatic prostate cancer after radical prostatectomy (RP) in patients followed expectantly for rising prostate-specific antigen (PSA) (noncastrate metastases).
Methods: Cox proportional hazards analyses were used to assess predictors of survival among 95 patients who developed clinically detectable noncastrate metastases after RP. The initial metastatic phenotype was characterised as minimal (nodal or axial skeletal involvement) or extensive (appendicular skeletal involvement or visceral metastases). Estimates of survival after diagnosis of metastases were generated with the Kaplan-Meier method.
Results: Median disease-specific survival from diagnosis of noncastrate metastases was 6.6 yr (95% confidence interval [CI], 5.2, 7.9). The initial site of metastatic disease was bone, lymph node, and viscera in 63%, 36%, and 6% of patients, respectively. Thirteen patients (14%) had extensive disease at their first metastatic manifestation. Longer PSA doubling time in the rising PSA state (hazard ratio [HR] 0.8 for each month increase in doubling time; 95% CI, 0.67-0.94) and the initial metastatic phenotype (HR 0.3 for minimal vs. extensive disease; 95% CI, 0.1-0.6) were associated with improved survival. The prostatectomy Gleason score, lymph node status at RP, PSA level at diagnosis of metastases, and interval from surgery to diagnosis of metastases did not correlate with outcome.
Conclusion: Men who develop noncastrate metastases after RP may have a durable survival. Favourable prognostic indicators include longer PSA doubling time preceding diagnosis of metastases and initial involvement of axial skeleton or lymph nodes.

Editorial Comment

What happens to patients with metastatic prostate cancer without hormonal deprivation (noncastrate metastases)? These patients nowadays are quite rare and it is very interesting to read this article on 95 patients who developed metastases after radical prostatectomy (RP) and were not castrated.

The time from operation to development of metastases was 3.2 years median, and the median cancer-specific survival thereafter was 6.6 years.

Interestingly, in these patients neither Gleason sum score nor lymph node status at RP, PSA level at diagnosis of metastases correlated to outcome. In contrast, fast premetastatic PSA doubling time and extensive (that is, fast) development of metastases were indicators of poor survival.

The authors propose a flow diagram which may be helpful to identify patients with high risk for the development of metastases in which the first identifier of poor outcome is PSA doubling time < 3 months.

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Impact of diagnostic delay in testis cancer: results of a large population-based study

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Eur Urol. 2007; 52: 1710-6

Objective: Testis cancer is the most common cancer in young men, and its incidence continues to rise. Even if prognosis is considered as good, a group with bad prognosis still remains. Diagnostic delay (DD), defined as the time elapsing from the onset of tumour symptoms to the day of diagnosis, is a way to evaluate the rapidity of diagnosis. We assessed the relationship between DD, disease stage, and survival rate.
Methods: A series of 542 patients diagnosed with a germ cell tumour between 1983 and 2002 at health facilities in the Midi-Pyrenees region, southwest France, were asked about DD. We analysed DD together with data regarding the disease (histologic type, stage), its treatments, and prognosis (impact on survival).
Results: Mean DD was longer in seminoma (4.9 +/- 6.1 mo) than in non-seminomatous germ cell tumour (NSGCT; 2.8 +/- 4.0 mo). DD was correlated with disease stage for the whole population ($p = 0.014$) and for NSGCT ($p = 0.0009$), but not for seminoma. DD had a significant impact on the 5-yr survival rate in the overall population ($p = 0.001$) and in the NSGCT group ($p = 0.001$), but not in the seminoma group. Global trends in mean DD did not change over the 20-yr study period, but we observed a slight decrease during the last decade.
Conclusions: DD is highly correlated with stage and survival in NSGCT. Urologists should promote programmes to enhance awareness and knowledge of testis cancer, so the diagnosis can be made more rapidly.

Editorial Comment

The authors report on the impact of diagnostic delay on ultimate outcome on survival. They report on a large cohort of 542 patients over a time of 20 years. This paper shows quite impressively that testicular tumors are often neglected by the patients for longer periods. Differences between seminomas and non-seminomatous germ cell tumors (NSGCT) certainly relate to the different growth rates between these tumors and how fast the patient begins to feel uncomfortable with this unclear process in his scrotum. In fact, diagnostic delay in NSGCT resulted in a significantly impaired survival. The authors state correctly that consequently, testis cancer awareness programs should be promoted and young men should be educated in scrotal self-examination.

One final question however was not addressed in this paper, that is the role of the physician. Was there any significant delay between first visit to a physician and diagnosis? Any differences between general practitioner and urologist?

I recommend thorough reading of this article.

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NEUROUROLOGY & FEMALE UROLOGY

Determining the course of the dorsal nerve of the clitoris

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Urology. 2008; 72: 1040-3

Objectives: To describe the course and variation of the dorsal nerve of the clitoris (DNC) to better define its anatomy in the human adult before embarking on therapeutic strategies in this region of the body and as an aid to surgeons to help avoid iatrogenic injury to the DNC during vaginal surgical procedures.
Methods: Six human female cadavers of variable body weights were sectioned. A vertical midline incision from the base of the clitoris extending toward the direction of the umbilicus was made. The DNC was identified by dissecting out the fascia, fat, and muscles around it. The anatomy of the nerve was noted bilaterally.
Results: Distally, the DNC pierced the perineal membrane lateral to the external urethral meatus. It traversed along the bulbospongiosus muscle before traversing posterior to the crura. The DNC reappeared, hooking over the crura to lie on the anterolateral surface of the body of the clitoris, before dividing into 2 cords and terminating short of the tip of the glans clitoris.
Conclusions: The results of this study have demonstrated the unique anatomy of the distal part of the DNC. Knowledge of the anatomy of the DNC, which was consistent for all the cadavers, is important so that surgeons can avoid potential iatrogenic injuries to this structure.

Editorial Comment

The authors describe the anatomy of the dorsal nerve of the clitoris with emphasis on its exit point from the perineal membrane to its end point bifurcation. Of note is that the authors found that the course of the dorsal nerve of the clitoris was in a position that would not be affected by traditional retropubic suburethral sling operation or a transobturator suburethral sling. In addition, they noted that the nerves ended on the lateral positions of the body of the clitoris at approximately 11 and 1 o'clock with no innervation noted at the dorsal position (12 o'clock) and the nerve did not reach the tip of the clitoris but terminated approximately 1cm short of the end.

This article is well worth reviewing prior to the performance of a transvaginal urethrolysis, especially when considering the suprameatal technique (1). It will be interesting to see if there is any affectation of this nerve with the increasingly popular non-surgical transurethral radiofrequency treatment for female stress urinary incontinence (2). The illustrations are excellent in quality and impart good recollective information. In addition to considerations for surgical technique, their anatomic description may impart valuable information to those physicians counseling couples with sexual dysfunction (especially with regard to the second phase female sexual function, arousal, as described in the commentary of the manuscript) and potential optimal sites for clitoral nerve stimulation.

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Urinary symptoms before and after female urethral diverticulectomy--can we predict de novo stress urinary incontinence?

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J Urol. 2008; 180: 2088-90

Purpose: We assessed preoperative and postoperative urinary symptoms, and determined risk factors for de novo stress urinary incontinence after transvaginal urethral diverticulectomy.
Materials and Methods: We reviewed the case records of 25 consecutive women who had transvaginal urethral diverticulectomy. Urinary symptoms were documented before and after surgery with a structured history and examination pro forma. Demographic, clinical and imaging parameters were reviewed to determine any association with preoperative and postoperative symptoms as well as possible risk factors for postoperative stress urinary incontinence.
Results: The most common presenting symptoms were urinary urgency and frequency (60%), and dyspareunia (56%). On physical examination the most common findings were a tender anterior vaginal wall mass (88%) and urethral discharge (40%). At a mean followup of 15.1 +/- 14.9 months (median 12) the rate of urgency-frequency symptoms and dyspareunia decreased significantly from 60% to 16% and from 56% to 8%, respectively. All the patients who had urge incontinence were cured of this symptom after the operation. De novo stress urinary incontinence developed in 4 patients (16%) postoperatively, and it was mild and only necessitated surgical treatment in 1 patient. A diverticulum larger than 30 mm and proximal urethral location were significant factors ($p < 0.05$) for the development of de novo stress urinary incontinence.
Conclusions: Irritative bladder symptoms are common in woman with urethral diverticulum and usually resolve after surgical excision. Stress urinary incontinence developed immediately after the operation, and had a significant association with a proximal urethral location and ultrasonically measured size greater than 30 mm.

Editorial Comment

The authors review their experience of 25 consecutive women who underwent a transvaginal urethral diverticulectomy. Special emphasis was placed on presenting signs and symptoms as well as the postoperative incidence of de novo stress urinary incontinence. The authors found that diverticuluae of a size > 30 mm and with a proximal urethral location had a higher association with postoperative stress urinary incontinence. The surgeons noted that all the patients who had urge incontinence were relieved of that symptom with the operation.

The authors shed light on their thoughts on urethral diverticulectomy especially with regards to symptoms and signs before and after the surgery. Of interest is that none of the patients appears to have had a preoperative MRI but were diagnosed by ultrasound. They did note that double balloon positive pressure urethrography also identified the diverticulum well when used (in 14 of the 25 patients) but cystourethroscopy could only identify the diverticular orifice in less than half of the patient population (44%). The authors reported a 16% de novo incidence of stress urinary incontinence and did not recommend a prophylactic anti-incontinence operation even for those patients meeting the criteria that were identified in the manuscript. Their median follow up was approximately 12 months. One wonders whether the incidence of de novo stress urinary incontinence will be higher if this population of patients is revisited in two or three years from this time and the subsequent recommendation of no prophylactic surgery will change.

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PEDIATRIC UROLOGY

Early treatment of acute pyelonephritis in children fails to reduce renal scarring: data from the Italian Renal Infection Study Trials

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Pediatrics. 2008; 122: 486-90

Objectives: The American Academy of Pediatrics recommendation for febrile infants and young children suspected of having a urinary tract infection is early antibiotic treatment, given parenterally if necessary. In support of this recommendation, data suggesting that delay in treatment of acute pyelonephritis increases the risk of kidney damage are cited. Because the risk was not well defined, we investigated renal scarring associated with delayed versus early treatment of acute pyelonephritis in children. Methods: The research findings are derived from 2 multicenter, prospective, randomized, controlled studies, Italian Renal Infection Study 1 and 2, whose primary outcomes dealt with initial antibiotic treatment and subsequent prophylaxis, respectively. From the 2 studies, we selected the 287 children with confirmed pyelonephritis on acute technetium-99m-dimercaptosuccinic acid scans who underwent repeat scanning to detect scarring 12 months later. The children were 1 month to < 7 years of age when they presented with their first recognized episode of acute pyelonephritis in northeast Italy.

Results: Progressive delay in antibiotic treatment of acute pyelonephritis from < 1 to >/= 5 days after the onset of fever was not associated with any significant increase in the risk of scarring on technetium-99m-dimercaptosuccinic acid scans obtained 1 year later. The risk of scarring remained relatively constant at 30.7 +/- 7%. Clinical and laboratory indices of inflammation were comparable in all groups, as was the incidence of vesicoureteric reflux.

Conclusions: Early treatment of acute pyelonephritis in infants and young children had no significant effect on the incidence of subsequent renal scarring. Furthermore, there was no significant difference in the rate of scarring after acute pyelonephritis when infants and young children were compared with older children.

Editorial Comment

Because of the long-term effects of pyelonephritis in children, including hypertension, proteinuria, and chronic renal failure, these authors studied whether early treatment of acute pyelonephritis diminishes renal scars in 287 children in a multicenter open-label parallel-group trial in Italian children, presenting with their first documented episode of acute pyelonephritis.

Initially the children were randomized to receive in one group either co-amoxiclav, or parenterally administered ceftriaxone. The second group was randomized to treat with antibiotic prophylaxis versus no treatment in a follow up study. Children were one month to seven years of age and acute pyelonephritis was the diagnosis when WBC > 25 cells/microliter in the urine, and a growth of a single organism of > 100,000 colonies in two consecutive tests as well as two or more of the following criteria: fever > 38°C, increased erythrocyte sedimentation rate or C-reactive protein level or neutrophil levels above normal for the age. Children are only included in the study with acute positive technetium DMSA scans performed within ten days of beginning antibiotic treatment and follow up scans 12 months later, and ultrasounds were also done.

There was no significant difference in the incidence of scarring with progressive delay and the initiation of antibiotic therapy from 1 to > 5 days after the onset of the fever. This was true for the subgroup of patients under two years of age. The scarring changes were found to be independent of early resolution of fever.

This article is discouraging in some respects since it has been long-held that prompt aggressive antibiotic treatment will diminish renal scarring in the setting of acute pyelonephritis. It would encourage the use of prophylactic antibiotics to prevent pyelonephritis except recent studies have cast a long shadow on the efficacy of prophylactic antibiotics to do this. Data also shows that the overall risk of scarring was independent of age between one month and seven years in this large study population. This would also suggest that early stoppage of prophylactic antibiotics and follow up in vesicoureteral refluxing patients may not be a wise choice also.

This is very good data in spite of the results confusing clinicians with older studies, it sheds light on the fact that this topic is one to be watched carefully in the future to guide further management.

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Undescended testis in older boys: further evidence that ascending testes are common

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J Pediatr Surg. 2008; 43: 1700-4

Introduction: We recommend orchiopexy between 9 and 18 months of age for surgical, testicular, and psychological reasons. However, in practice, we observed many patients coming to orchiopexy at a later age. To understand this difference better, we reviewed our experience with patients undergoing late orchiopexy.
Methods: We reviewed retrospectively the office medical records of all boys who had undergone an orchiopexy between July 1997 and April 2006. We defined a "late" orchiopexy as that performed at 4 years of age or later. Each boy was examined carefully by a pediatric urologist, and preoperative, intraoperative, and postoperative findings were reviewed.
Results: There were 191 late orchiopexies in 177 patients (from a total of 587 orchiopexies in 552 patients). Median age at the operation was 7.2 years (range, 4.0-16.2). Preoperatively, the testes were palpable in 140 (72%) and nonpalpable in 51 (28%). The apparent reason for the late orchiopexy was an ascending testis (previously descended) in 85 (45%), parental delay in 41 (22%), late referral in 39 (20%), and iatrogenic cryptorchidism in 18 (9%). Ascended testes were more likely to have a history of being retractile (85% vs. 30%), to have a patent processus vaginalis (78% vs. 54%), and to be localized to the superficial inguinal area (87% vs. 50%).
Conclusions: Primary care provider and parent education on the benefits of early orchiopexy is important, but in addition, ascending testes are much more common than previously thought. Patients with retractile testes should be followed regularly.

Editorial Comment

This manuscript explores orchiopexies in boys over four and compares them to patients who were under four years of age. 552 had 587 orchiopexies. 177 of these boys had 191 orchiopexies over the age of four. The stated reasons were ascending testicles in 45%, parental delay in 22%, referral or insurance problems in 20%, entrapped testes in 9%, with the remaining cases uncertain. 85% of the ascending testis group and 30% of the others had a history of retractile testes. Palpable testes were found in 93% of the ascending testes and only 58% of the other patients. The ascending testes were more likely to be found in the superficial inguinal pouch (87%) while only 50% of the other categories had the testicles in the superficial inguinal pouch with a statistical difference of $p < 0.001$. The processus vaginalis was more likely to be patent in the ascending testis

group (78%) than the other group (54%) with a p-value of < 0.001. Excluding the iatrogenic group where the testes were stuck with scar tissue, the p-values were still significant.

It is becoming better understood that some testes that were found in the scrotum ascend and become fixed in a non-scrotal position. It is interesting to note that the ascending testes are more likely to be in the superficial inguinal pouch and more likely to have a patent processus vaginalis than the other delayed orchiopexy patients. It is still important for urologists to recognize that early orchiopexy before the second year of life has significant benefit. Educating primary care physicians and referring physicians about early referral is still the best policy.

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