

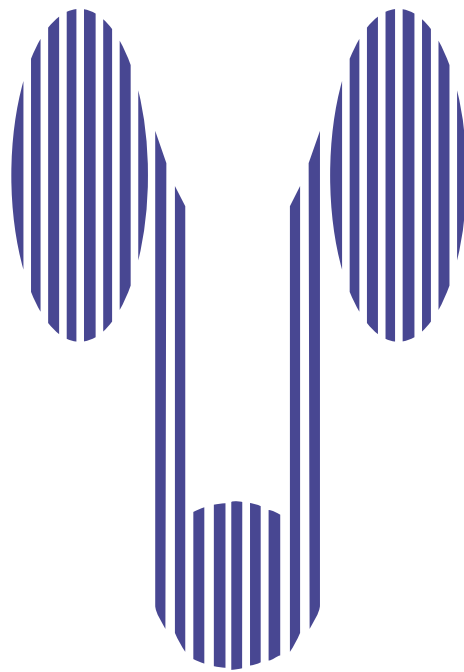


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EDITOR'S COMMENT

The September – October 2006 issue of the International Braz J Urol presents interesting contributions from different countries, and as usual, the Editor's Comment highlights some papers.

Doctor Manoharan and colleagues, from University of Miami School of Medicine, Miami, Florida, USA, examined on page 529 the patients undergoing radical cystectomy with orthotopic neobladder to determine whether adjuvant chemotherapy in this group is safe. Over a 12 year period, 136 patients underwent radical cystectomy and orthotopic neobladder construction for bladder cancer. Of these, 83 patients were at high risk for recurrence. Nineteen patients received adjuvant chemotherapy and 64 did not. The complication rate in the adjuvant chemotherapy group was 53% and it was 23% in those who did not receive chemotherapy. There were no peri operative or treatment related death. The authors concluded that adjuvant chemotherapy is a safe treatment for patients undergoing radical cystectomy and orthotopic neobladder substitution. Hence, the option of orthotopic neobladder should not be denied in selected bladder cancer patients with high risk for recurrent disease.

Doctor Cheng and co-workers, from The Chinese University of Hong Kong and Prince of Wales Hospital, Hong Kong, China, studied on page 536 the long-term outcome of radical cystectomy for transitional cell carcinoma and evaluated prognostic factors for disease specific survival. The study included 133 cystectomies with a median follow up of 20 months. After univariate analysis, pT stage, N stage, lymph node density, carcinoma in-situ, surgical margin and post-operative radiotherapy to distant metastasis were predictive of disease specific survival. On the other hand, with multivariate analysis, only pT stage, lymph node density and post-operative radiotherapy to distant metastasis were predictive of disease specific survival. Patients with lymph node density 20% or below showed better disease specific survival. The authors concluded that pT stage and lymph node density were the most important predictive factors for disease specific survival after cystectomy in the Chinese population. Dr. Hammad M. Ather, from Aga Khan University Hospital, Karachi, Pakistan, Dr. John Peter Stein, from University of Southern California, Los Angeles, USA and Dr. Stephen D. Beck, from Indiana University School of Medicine, Indianapolis, Indiana, USA, provided interesting editorial comments on this paper.

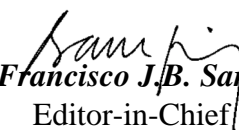
Doctor Hadziselimovic, from the Kindertagesklinik Liestal, Liestal, Switzerland, assessed on page 570 the incidence of Ad spermatogonia (stem cells for fertility) in 20 cryptorchid patients, all of whom had a successful orchidopexy in childhood but developed azoospermia following puberty. The patients were classified into 2 groups according to the time of surgery: A = less than 21 months of age (n = 5, mean = 10.7 ± 8.6 months) and B = during childhood (n = 15, mean = 10.1 ±

EDITOR'S COMMENT - *continued*

3 years). The author found that in group A, all patients had germ cells at the time of surgery (mean = 1.04 ± 1.4 germ cells per tubular cross section); only 6 patients in group B (40%) had no germ cells (mean = 0.17 ± 0.4); A vs. B, $p = 0.0133$. Importantly, Ad spermatogonia were absent in the entire study population. The plasma FSH of 16 patients (80%) was abnormal while the plasma testosterone of all the patients was normal. The author concluded that the most severe cause of infertility in cryptorchid patients cannot be mitigated by an early successful surgery alone.

Doctor Quintela and co-workers from Belo Horizonte, Minas Gerais, Brazil, reported on page 521 their experience with 43 retroperitoneal laparoscopic nephrectomy for benign kidney disease. Retroperitoneoscopy was performed with 4 trocar port technique in a lateral position. The approach to vascular pedicle was done posteriorly and vessels were clipped by metal and Hem-o-lock. The sample was intact extracted in an Endo-Bag prolonging one trocar incision. The median operative time was 160 minutes and median blood loss was 200 mL. Four cases (9%) were converted to open surgery. The authors concluded that retroperitoneoscopy offers a safe, effective and reproductive access to nephrectomy for benign pathologies. Dr. Jonas Wadström, from Uppsala University Hospital, Sweden, Dr. K. Mita, from Hiroshima University, Japan, Dr. A. Terai, from Kurashiki Central Hospital, Japan and Dr. David A. Goldfarb, from Cleveland Clinic Foundation, USA, provided interesting editorial comments on this paper.

Doctor Petrou and colleagues, from the Mayo Clinic Jacksonville, Florida, USA, evaluated on page 578 the patient preference for injectable therapy over surgery in the treatment of female urinary incontinence. After evaluating 58 female patients the authors found that the mean lowest acceptable success rate for all 58 surveyed patients was 34%, with 23 (40%) accepting a success rate of only 10%. The data suggested that older patients might tend to accept lower success rates than younger patients (mean of 39% for patients aged less than 60 years compared to 22% for those aged 80 years or older). It was concluded that patients appear willing to accept a relatively low success rate for injectable therapy compared to open surgery.


Dr. Francisco J.B. Sampaio
Editor-in-Chief

Laparoscopic Surgery in Urological Oncology: Brief Overview

Jose R. Colombo Jr, Georges P. Haber, Mauricio Rubinstein, Inderbir S. Gill

Section of Laparoscopic and Robotic Surgery, Glickman Urological Institute, The Cleveland Clinic Foundation, Cleveland, Ohio, USA

ABSTRACT

The authors report the experience of a high-volume center with laparoscopic surgery in urological oncology, as well as a review of other relevant series. Laparoscopic outcomes in the treatment of adrenal, kidney, upper tract transitional cell carcinoma, bladder, prostate, and testicular malignancy are described in this review. Specific considerations as complications and port-site recurrence are also addressed. The authors concluded that the intermediate-term oncological data is encouraging and comparable to open surgery.

Key words: urological neoplasms; treatment; laparoscopic surgery; complications
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INTRODUCTION

Initially described for the treatment of kidney cancer (1), laparoscopic approach has rapidly evolved in the urological oncologic field. This relatively new surgical technique is part of the urologist's armamentarium in treating adrenal, upper tract transitional cell carcinoma, bladder, prostate, and testicular malignancy. The laparoscopic technique duplicates open surgery oncological principles, associating the benefits of minimally invasive approach. Herein, the authors present their experience in laparoscopic surgery for urological cancer at The Cleveland Clinic, and review other relevant series.

KIDNEY CANCER

Laparoscopic radical nephrectomy (LRN) is considered the standard treatment for most patients

with renal malignancies that are not eligible to nephron-sparing surgery. Major advantages of LRN over open radical nephrectomy include decreased perioperative morbidity, lower blood loss, shorter hospital stay, and quicker convalescence (2,3). Reports available in literature have showed comparable results between laparoscopic and open radical nephrectomy, with projected 5-year cancer-specific survival of 87% to 98% in the laparoscopic series, and overall survival of 81% to 94% (4-8) (Table-1). In 63 consecutive patients undergoing LRN at our institution, estimated 7-year overall and cancer-specific survival was 72% and 90%, similarly to a contemporary series of open radical nephrectomy.(9) For T1 tumors (≤ 7 cm) the estimated 7-year cancer-specific survival in the laparoscopic group was 97% vs. 96% in the open group ($p = 0.84$), and for T2 tumors (> 7 cm) the estimated 7-year cancer-specific survival in the laparoscopic group was 66% vs. 87% in the open group ($p = 0.26$). No contralateral

Table 1 – Laparoscopic radical nephrectomy oncological outcomes.

Author	N	Follow-up (years)	Blood Loss (mL)	Operative Time (hours)	Hospital Stay (days)	Estimated 5-year Cancer-Specific Survival
Dunn et al. 2000 (3)	44	2.1	N/A	5.5	3.4	91%
Chan et al. 2001 (4)	66	2.9	280	4.2	3.8	95%
Ono et al. 2001 (5)	102	2.4	254	4.7	N/A	95%
Portis et al. 2002 (6)	64	4.5	219	N/A	4.8	98%
Saika et al. 2003 (7)	195	3.3	248	4.6	N/A	87%
Permpongkosol et al. 2005 (8)	121	6	280	4.2	3.8	94%*
Colombo et al. 2006 (9)	48	5.4	179	2.8	1.4	91%*

Adapted from Colombo et al. (9); * actual 5-year survival; N/A: not available.

recurrence was found during the follow-up in this series, this is likely due to the relative small number of patients, low positive margin rate, and small incidence of multifocality. Renal function in this series, decreased significantly after radical nephrectomy; however, this was not affected by the surgical approach.

Retroperitoneal is our preferred access, except in cases of larger tumors (> 10 cm) and previous retroperitoneal surgery. Prospective randomized studies comparing the transperitoneal and retroperitoneal approaches concluded that there is no statistical difference between the techniques (10,11).

For appropriate histopathological analysis, the specimen is always extracted intact in an adequate laparoscopic bag. Financial analysis performed at our institution concluded that laparoscopic radical nephrectomy is 12% less expensive than open radical nephrectomy once the learning curve is reached (12).

In patients with metastatic renal cell carcinoma, the laparoscopic cytoreductive nephrectomy can be performed with low morbidity, smaller blood loss, and shorter hospital stay. The minimally invasive technique may shorten the interval between the nephrectomy and start of systemic therapy (13).

Partial nephrectomy for renal cancer was initially indicated for patients with compromised renal function, solitary kidney, and bilateral tumor. Since, long-term oncological outcomes haven been

demonstrated as equivalent to radical nephrectomy while preserving renal function (14), indications of partial nephrectomy has expanded to patients with normal contralateral kidney. Laparoscopic partial nephrectomy (LPN) has emerged as a minimally invasive alternative to partial nephrectomy in order to minimize the morbidity of the open procedure (15). LPN was limited to patients with small, superficial, solitary, and peripheral tumors. With increasing experience, LPN is now performed for larger, central and hilar tumors. In our study with 100 patients, each with at least 3-years follow-up, overall survival was 86% and cancer-specific survival was 100% (16). Fifty of these patients, have reached 5-years follow-up, with overall and cancer-specific survival of 84% and 100%, respectively (17) (Table-2). Hilar clamping is used to provide a bloodless field during tumor excision and pelvicaliceal repair. The impact of hilar clamping was evaluated and no clinical sequelae were observed with warm ischemia smaller than 30 minutes (18). Similar perioperative complication rate was found after LPN in patients with abnormal renal function (serum creatinine ≥ 1.5 mg/dL comparing to patients with normal renal function (19). While comparing the percentage decreasing in renal function, evaluated by serum creatinine and glomerular filtration rate, there was no significant difference between patients with abnormal and normal renal function. In this study, solitary kidney was an independent risk factor for hemodialysis.

Table 2 – Partial nephrectomy series oncological outcomes.

Author	N	Approach	Follow-up (months)	Tumor Size (cm)	Overall Survival	Cancer-Specific Survival
Lerner et al. 1996	185	Open	44	4.1	77%	89%
Belldegrun et al. 1999	146	Open	57	3.6	86%	93%
Hafez et al. 1999	485	Open	47	2.7	81%	92%
Moinzadeh et al. 2006 (16)	100	Laparoscopic	42	3.1	86%	100%
Lane & Gill 2006 (17)	50	Laparoscopic	62	3.0	84%	100%

Adapted from Lane & Gill (17).

ADRENAL CANCER

Although laparoscopic approach has become the gold standard for benign surgical adrenal disorders such as Cushing's disease, aldosteronoma, and pheochromocytoma, only few reports addressing laparoscopic surgery for adrenal malignancy are available. In our institution more than 330 laparoscopic adrenalectomies were performed. Our experience with 31 patients with adrenal malignancy showed an estimated 5-year survival of 40%. In this study, local recurrence occurred in 7 patients (23%), and these patients had significantly decreased 3-year survival compared to those without local recurrence (16.7% vs. 66%, $p = 0.016$). The survival rate was not associated with gender, age, tumor size, or laparoscopic approach employed. There was no difference in survival for patients with solitary metastasis to the gland compared to those with primary adrenal malignancy. In this series, the 5-year survival was similar in patients with an adrenal tumor smaller than 5 cm vs. 5 cm or greater (36% vs. 46%, $p = 0.43$) (20). These results can be favorably compared to those in a prior open series with 37 patients undergoing open adrenalectomy for non-primary adrenal malignancy, with a 5-year actuarial survival of 24% (21). The suspicion of peri-adrenal infiltration is a contraindication for laparoscopic adrenalectomy. Tumor size per se is not a contraindication, although we generally limit laparoscopic adrenalectomy to tumors in the 10 cm range. Intraoperative concern regarding the adequacy of wide excision should lead to open conversion.

BLADDER CANCER

Radical cystectomy is the gold-standard treatment for organ confined muscle invasive or high-grade superficial recurrent bladder cancer (22). Laparoscopic approach for radical cystectomy is relatively new, and studies available in the literature show encouraging perioperative and short-term oncological data. Urinary diversion can be performed either intracorporeally ("pure laparoscopic") or through a 5-7 cm mini-laparotomy incision ("laparoscopic assisted"). A series with 37 patients undergoing laparoscopic radical cystectomy in our institution with a mean follow-up of 31 months (1-66 months) showed an estimated 5-year overall and cancer-specific survival of 58% and, 68%, respectively (23). Both overall and cancer-specific survivals were superior in organ confined vs. non-organ confined disease and node-negative vs. node-positive disease. Overall survival was superior when an extended lymphadenectomy (median number of nodes = 21) is performed, compared to patients undergoing limited template lymphadenectomy (median number of nodes = 6). Cancer-specific survival trended towards to a slightly improvement; however, this did not reach statistical significance, likely due to smaller number of patients (Table-3). When comparing "pure laparoscopic" technique to "laparoscopic-assisted" technique we found that the morbidity of laparoscopic radical cystectomy is largely due to the urinary diversion procedure. Our data support the extracorporeal performance of the bowel work and ureteroileal anastomoses.

Table 3 – Sub-group analysis of overall and cancer-specific survival in 37 patients undergoing laparoscopic radical cystectomy.

Final Pathology	N	Mean Follow-up (months)	Overall Survival	Cancer Specific Survival
pT1	11	27	61%	100%
pT2	12	36	91%	100%
pT3	10	29	45%	85%
pT4	4	28	25%	66%
p Value			0.08	0.21
Organ confined	23	32	77%	100%
Non-organ confined	14	28	31%	76%
p Value			0.01	0.03
Concomitant CIS	8	25	41%	55%
No CIS	24	33	81%	100%
p Value			0.03	0.002
pN0	30	32	74%	100%
pN1	7	27	25%	33%
p Value			0.02	0.002

Adapted from Haber & Gill (23); CIS = carcinoma in situ.

Laparoscopic-assisted radical cystectomy is technically more efficient, associated with a quicker recovery profile, and decreased complication rate (24) (Table-4).

PROSTATE CANCER

Radical prostatectomy has been shown to improve cancer-specific survival in the context of a randomized trial (25). The laparoscopic approach offers the advantage of magnification of the surgical field, allowing a clear operative field with better view during the dissection of the neuro-vascular bundles and urethro-vesical anastomosis. Transrectal real-time Doppler ultrasound is routinely performed in our institution during the procedure to identify the neuro-vascular bundle and the prostatic edges. This technique decreased significantly the overall positive margin rate (29% vs. 9%, $p < 0.001$), and

predicted the presence of pT₂ and pT₃ disease in 85% and 85% of cases, respectively (26). In a series of 1000 laparoscopic radical prostatectomies published by Guillonneau et al. (27), the positive margin rate was 6.9%, 18.6%, 30% and 34% for pT2a, pT2b, pT3a, and pT3b, respectively. Overall 3-year biochemical progression-free survival was 90.5%, ranging from 44% to 91% according to the pathological stage. Rassweiler et al. (28) published their early 180-case experience with 16% of positive margins, and 95% biochemical progression-free survival. Early oncological results of laparoscopic radical prostatectomy are comparable to the open approach, but studies with long-term follow-up are still lacking.

Salomon et al. (29) reported a potency and continence rate of 59% and 90%, while. Guillonneau et al. (30) reported a potency and continence rate of 85%, and 82% after a period of 12 months (Table-5).

Table 4 – Laparoscopic radical cystectomy with urinary diversion. Pure laparoscopic vs. laparoscopic assisted.

Urinary Diversion	Pure Laparoscopic	Laparoscopic Assisted	p Value
Number	17	20	
Operative time (hours)	9.38	7.35	< 0.001
Blood Loss (cc)	788	472	0.01
Transfusion	4	1	0.10
Oral Intake (days)	6	2.8	0.01
Ambulation (days)	16.8	2.46	0.02
Major complications	29.4%	5%	0.04
Late complications	17.6%	20%	0.86

Adapted for Haber et al. (24)

UROTHELIAL CANCER

Laparoscopic nephroureterectomy with en bloc bladder cuff for upper tract urothelial carcinoma appears to have similar oncological outcomes comparing to open nephroureterectomy, regarding positive margin rate, and bladder, local and distant recurrences (31). Operative time and perioperative complication rate are equivalent, with less blood loss, less analgesic use, and shorter hospitalization, avoiding the usual two incisions of the open nephroureterectomy (31,32). At least five methods for controlling the distal ureter and bladder cuff were described, including endoscopic, laparoscopic and open. The most commonly used is the open technique, through a low Gibson incision. This method avoids patient repositioning, minimizing tumor spillage with ureteral clipping early in the procedure, right after

renal hilum control. To decrease the presence of ureteric stump, it is recommended to dissect laterally to the bladder until visualization of the ureteral hiatus, performing the resection of bladder cuff under direct vision (32).

Matin & Gill (33) reported a different recurrence and survival rates related to the surgical technique employed to control the distal ureter and bladder cuff. The cystoscopic detachment and ligation of the bladder cuff was significantly associated to a better survival when compared to the laparoscopic extravesical stapling with cystoscopic deroofting and fulguration of the intramural ureter.

In a multicenter study with 116 patients undergoing laparoscopic nephroureterectomy for upper tract transitional cell carcinoma, the mid-term results were comparable to the open series (34). The 2-year overall survival according to the pathologic

Table 5 – Laparoscopic radical prostatectomy series oncological outcomes.

Author	N	Gleason Score	PSA (ng/mL)	Positive Margins		Biochemical Progression-Free			
				pT2	pT3	pT2a	pT2b	pT3a	pT3b
Guillemot et al. 2003 (27)	1000	N/A	10	6-18%	30-34%	91.8%	88%	77%	44%
Rassweiler et al. 2005 (28)	500	6	11.7	7.4%	31.8%	95.9%		88%	
Solomon et al. 2002 (29)	137	5.7	11.6	21.9%	40.8%	90.4%		56.8%	

N/A: not available.

grade was 88%, 90%, 80% and 90% for grade I, II, III, IV, respectively. The 2-year cancer-specific survival was 89% for pT1, 86% for pT2, 77% for pT3, and 0% for pT4. Although long-term follow-up data is not available yet, the mid-term data support the use of minimally invasive technique to treat upper tract transitional cell carcinoma.

TESTICULAR CANCER

When indicated, standardized retroperitoneal lymph node dissection (RPLND) can be performed for Stage I and low-volume Stage II disease using laparoscopic access, even after chemotherapy. Both staging and therapeutic techniques are currently performed with minimal morbidity (35,36). The long-term results reported by Steiner et al. (36) are similar to the open series. In this study, the antegrade ejaculation was preserved in 98% of patients, with significantly lower morbidity.

RPLND after chemotherapy represents a technical challenge. The complication rate for this procedure is still high, and it should be performed by only very experienced laparoscopic surgeons (37). Janetschek et al. described their experience with 35 patients undergoing postchemotherapy laparoscopic RPLND, with chylous ascites occurring in 6 cases. In their institution, a preoperative low-fat diet is now used 1 week before and 2 weeks after the surgery (38).

CONSIDERATIONS

Perioperative Complications

Analyzing 1867 laparoscopic procedures for urological malignancy at our institution, the perioperative complication rate was 12.3% (95% CI 10.9 to 13.8) (39). Intraoperative complications occurred in 4.9% (95% CI 4.0 to 6.0), including hemorrhage (3.6%), and visceral injury (1.2%). Because of these complications, 18 (0.9%) cases were converted to open procedure. Postoperative complications have been noted in 162 (8.6%) cases, and the most common were hemorrhage in 52 (2.7%),

acute renal failure in 16 (0.8%), and pneumonia, pulmonary embolism, pulmonary edema, atrial fibrillation in 7 (0.3%) cases each. Perioperative mortality occurred in 8 cases (0.4%). Radical cystectomy (adj. OR 4.9, 95% CI 1.3 to 8.0; $p < 0.001$), length of surgery greater than four hours (adj. OR 2.5, 95% CI 1.7 to 3.8; $p < 0.001$), partial nephrectomy (adj. OR 2.4, 95% CI 1.5 to 3.8; $p < 0.001$), and serum creatinine ≥ 1.5 mg/dL (adj. OR 2.1, 95% CI 1.0 to 4.3; $p = 0.04$) were found as independent predictors for perioperative complication. The length of hospitalization increased directly proportional to the number of complications ($p < 0.001$).

Literature supports the importance of experience of the surgeon and hospital-volume in the treatment of cancer. Begg et al. (40) found that perioperative mortality in complex open oncologic procedures is lower when performed by surgical team with higher volume. In study addressing exclusively open radical prostatectomy (41), the same author concluded that postoperative complication rate is significantly reduced when the operation is performed in a high-volume hospital and by an experienced surgeon. In our study, surgeon's experience was not an independent predictor for perioperative complication ($p = 0.07$), although we identified a trend pointing to it. After 50 cases of laparoscopic surgeries for urological malignancy the adjusted odds ratio was 0.97. When increasing this experience to 100 cases and 500 cases, the odds ratio were 0.96 and 0.80, respectively. We believe that multicentric studies with a larger number of procedures would show the same result for laparoscopic procedures as well.

Port-Site Recurrence

Port site metastasis, intraperitoneal dissemination, and local recurrence represent a major concern when laparoscopic approach is employed. Port-site recurrence is influenced by local and systemic immunological status, tumor behavior and technical factors (42). Activation of cytokines (IL-1 and IL-6), C-reactive protein, and polymorphonuclear leukocytes occur in a smaller level after a laparoscopic procedure compared to similar open procedure (42,43). Some studies showed a better preservation

of cell-mediated immunity after laparoscopic surgery (44,45). However, these benefits are not applied to the peritoneal level, possibly related to the hypoxic environment due to pneumoperitoneum pressure and secondary effect of the carbon dioxide in the peritoneal macrophage response (35-37).

In a series with over 1000 laparoscopic cases, Rassweiler et al. (42) found eight cases of local recurrence and 2 port sites metastasis. In the multicentric study by Micali et al. (46) with 10912 laparoscopic surgeries for cancer, 10 cases of port seeding, and 3 cases of peritoneal tumor spreading were found. Aggressiveness of tumor, deficient immunological state of the oncological patient, and poor oncological principles related to specimen extraction are responsible for these rare events (42,46).

In attempting to minimize the risks for port-site and local recurrence, tumor violation and spillage should be avoided by using the appropriated surgical technique, including the use of impermeable bags during specimen extraction, and removal of tumor-contaminated instruments from the operative field after the target-organ entrapment.

CONCLUSION

Although long-term oncological outcomes are not available for the majority of genitourinary malignancies treated by the laparoscopic approach, the intermediate-term data are encouraging and comparable to open surgery. Multicentric studies with longer follow-up are necessary to validate this relatively new surgical approach.

CONFLICT OF INTEREST

None declared.

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Correspondence address:

Dr. Inderbir S. Gill
Section of Laparoscopic and Robotic Surgery
The Cleveland Clinic Foundation
9500 Euclid Av, A100
Cleveland, OH 44195, USA
Fax: +1 216 445-7031
E-mail: gilli@ccf.org

Transdermal Drug Delivery Treatment for Overactive Bladder

Roger R. Dmochowski, Jonathan S. Starkman, G. Willy Davila

Vanderbilt University Medical Center (RRD, JSS) and Section of Urogynecology and Reconstructive Pelvic Surgery (GWD), Cleveland Clinic Florida, Weston, Florida, USA

ABSTRACT

Overactive bladder is commonly treated with oral anticholinergic drugs such as oxybutynin chloride. Although oral anticholinergic agents have been effective in controlling urinary urgency and incontinence, adverse events, particularly dry mouth, often cause patients to discontinue oral therapy and to endure incontinence. Oxybutynin can be delivered transcutaneously, maintaining the efficacy of oral oxybutynin while significantly minimizing side effects (e.g., dry mouth) that may complicate therapy. By avoiding hepatic and gastrointestinal metabolism of oxybutynin, less N-desethyloxybutynin (N-DEO) is produced and this compound is deemed to be responsible for anticholinergic side effects such as dry mouth. This novel oxybutynin formulation offers patients with OAB and urge urinary incontinence a well-tolerated option for managing the symptoms of overactive bladder.

Key words: *overactive bladder; oxybutynin; administration, cutaneous; urinary incontinence*
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INTRODUCTION

Overactive bladder (OAB) syndrome is a common symptom complex that affects as many as 33 million Americans and more from across the world (1). Management of OAB has become standardized to some degree as pharmacotherapy coupled with behavioral techniques is usually considered first line treatment (2-4). Despite the existence of effective therapy for OAB, at any given time only a fraction of patients is receiving therapy. Reasons for this disparity are likely multifactorial, and include issues related to cost of therapy, patient and physician attitudes, a heterogeneous patient population with respect to symptom severity and response to therapy, and side effects related to drug therapy. When assessing the various pharmacotherapies for OAB, anti-cholinergic

medications are currently considered standard of care. Efficacy of drug therapy is achieved via muscarinic receptor blockade at the end organ level. Five muscarinic receptor subtypes (M1-M5) have been identified, the distribution of which varies depending on the particular organ system. In the bladder, the predominant receptors are the M2 and M3 subtypes. Although the M2 subtype is the most abundant receptor in the bladder, it appears that the M3 receptor subtype is most directly responsible for the symptoms of OAB as it mediates detrusor contractility (5-7).

Oral oxybutynin has been the most commonly prescribed treatment for OAB for nearly 30 years. In recent years, a number of alternatives have been introduced, including tolterodine, trospium, solifenacin, and darifenacin. Extended release formulations of oxybutynin and tolterodine result in

controlled release of drug and steady plasma concentrations, improving tolerability compared to immediate-release (IR) dosing (8-10). Despite this, the major limitation of pharmacotherapy for OAB remains the significant incidence of anti-cholinergic side effects secondary to antagonism of muscarinic receptors at the level of the salivary gland, gastrointestinal tract, and central nervous system (11,12). These adverse effects negatively impact patient compliance and overall quality of life, often leading to patient initiated discontinuation of drug therapy.

NOVEL DELIVERY

Intrarectal, intravesical, and intravaginal oxybutynin have been administered in clinical trials in an attempt to avoid first-pass hepatic metabolism of the drug (13-17). In one study, intrarectal oxybutynin was shown to be efficacious and more tolerable than oral oxybutynin (13), while another study demonstrated that a significant number of patients still experience adverse events (dry mouth and constipation) (14). Intravesical oxybutynin administered via catheterization has shown acceptable efficacy and tolerability in several studies. One study showed that aqueous oxybutynin 2-3 times daily eliminated or significantly reduced urge incontinence episodes in 55% of the patients (16). Another small study demonstrated improvement in cystometric parameters and patient satisfaction with modified intravesical oxybutynin (intravesical oxybutynin with hydroxypropylcellulose, 5 mg/10 mL) (18). While the clinical studies showed that there were minimal anticholinergic side effects affecting patient tolerability, inconvenience with self catheterization and treatment induced symptoms of cystitis may limit widespread acceptance of intravesical oxybutynin therapy (19). Furthermore, there may be issues related to contaminants involved in the preparation of aqueous oxybutynin for intravesical delivery. Despite observed clinical efficacy, there are no commercial preparations of oxybutynin rectal suppositories available and intravesical oxybutynin would only appear reasonable in patients performing intermittent

self catheterization, making it an inconvenient option for most patients with OAB. Randomized clinical trials evaluating safety and efficacy of an oxybutynin vaginal ring delivery system are currently ongoing.

There have been significant improvements in transdermal drug delivery systems, moving away from older liquid reservoir systems to current matrix type patches and aqueous gels. Advantages of transdermal systems in general include the avoidance of the gastrointestinal tract and first-pass hepatic metabolism, in addition to allowing drugs with relatively poor bioavailability to attain therapeutic serum levels at low dosages. Currently, a number of transdermal medications are available commercially including testosterone, estrogen, fentanyl, scopolamine, clonidine, nicotine, and oxybutynin (20).

OXYBUTYNIN MECHANISM OF ACTION

Oxybutynin (OXY) is a tertiary amine that exists commercially as a racemic mixture of R- and S- enantiomers. The mechanism of action of oxybutynin is 2-fold, consisting of 1) its anti-muscarinic properties and 2) its spasmolytic action on detrusor smooth muscle cells (21,22). Oxybutynin exhibits stereoselectivity, as R-OXY has greater anticholinergic activity compared to S-OXY. The spasmolytic effects on smooth muscle appear to be equal for the R- and S- isomers (23,24).

Transdermal oxybutynin (OXY-TDS) is a matrix-type patch composed of 3 layers consisting of a backing film (polyester/ethylene-vinyl acetate-PET/EVA), adhesive matrix layer (containing oxybutynin free base), and an overlapping release liner strip (Figure-1). The backing film (Layer 1) has an occlusive function, which serves to protect the adhesive/drug layer, while the release liner contains 2 overlapped silicone coated polyester strips. This system is applied to the skin after peeling off the plastic tab of the release liner. OXY-TDS contains 36 mg of oxybutynin and triacetin (permeation enhancer) dissolved in an acrylic block copolymer adhesive with a surface areas of 39 cm² (25). The average daily dose of oxybutynin absorbed from the 39 cm² Oxytrol™

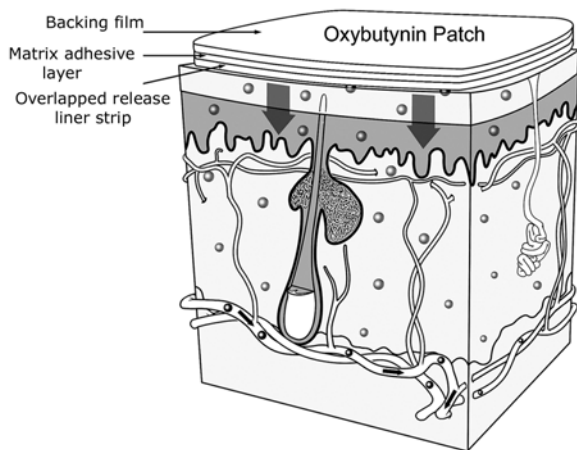


Figure 1 – Transdermal oxybutynin system.

system is 3.9 mg/day (0.1 mg/cm²). Absorption of drug requires penetration of the lipid rich stratum corneum of the skin and the more aqueous epidermis and dermis. Thus, oxybutynin must possess both lipophilic and hydrophilic properties. Once contact is established between the skin and OXY-TDS, diffusion of oxybutynin and the permeation enhancer occurs across the stratum corneum, controlled by the interaction of oxybutynin and enhancer with lipids in the skin (25). Oxybutynin is then absorbed by the capillary microcirculation in the dermis of the skin

and delivered into the systemic circulation, thus bypassing first-pass metabolism by the liver (Figure-1). Avoidance of hepatic metabolism reduces conversion of oxybutynin to its chief metabolite, N-desethyloxybutynin (N-DEO), which is thought to mediate much of the adverse anticholinergic side effects attributed to OXY. The OXY-TDS patch can also be incised/cut prior to application to improve tolerability without compromising efficacy. Potential benefits of transdermal oxybutynin include the avoidance of pre-systemic metabolism in the gut and liver (25,26) (Table-1).

OXYBUTYNYN PHARMACOKINETICS

Following oral administration, oxybutynin undergoes extensive first-pass metabolism in the liver, with an additional portion metabolized within the lumen of the GI tract. As a result, the bioavailability after an oral dose of oxybutynin is only 6%. Hepatic metabolism (Cytochrome P450, CYP3A4) results in the conversion of oxybutynin (OXY) to N-desethyloxybutynin (N-DEO) and levels of N-DEO reach plasma concentrations that are between 4 and 10 times the concentration of native oxybutynin (27,28). Many of the anticholinergic side effects, particularly dry mouth, of oral oxybutynin are thought to be secondary to N-DEO, which has been shown in

Table 1 – Transdermal drug delivery systems.

Advantages

- Improves compliance. No pills to remember.
- Slow and steady release of drug results in more consistent plasma concentrations.
- Avoids first-pass hepatic and gastrointestinal metabolism.

Disadvantages

- Patients must change patch after defined dosage period.
- Requires careful disposal as patch may still contain active medication
- Limited number of drugs may be used by transdermal system.
- Local dermatologic reactions at the application site
- Difficulty with patch adhesion to skin occurs in limited number of cases
- Variable absorption secondary to individual skin characteristics and local dermal metabolism.

studies to bind to muscarinic receptors in the parotid gland with higher affinity than OXY (29). As there are only small amounts of CYP3A4 found in the skin, transdermal delivery of oxybutynin avoids pre-systemic metabolism and results in lower plasma levels of N-DEO. Thus, there is the potential for less anticholinergic adverse events.

A study by Zobrist et al. (25), evaluated the in vitro and in vivo pharmacokinetics and metabolism of transdermal oxybutynin. After initial transdermal application there is a 2-hour window until measurable plasma levels of drug are detectable, followed by a gradual increase in mean OXY and N-DEO plasma levels over a 24-36 hour time period, reaching average maximum concentrations of 3 to 4 ng/mL. Levels of drug then plateau and remain relatively stable for another 24 hours before declining throughout the remainder of the 96-hour dosing interval. Following the removal of the transdermal system there is a consistent and transient increase in plasma drug concentrations over 30 minutes, and a rapid decline in plasma concentrations thereafter. Another randomized crossover study by Zobrist et al. (26) evaluated the pharmacokinetics of the R- and S-enantiomers of oxybutynin following oral and transdermal administration. In vitro skin flux experiments reveal that there is equal absorption of R- and S- oxybutynin through the human epidermis with a mean ratio of R-OXY/S-OXY of 1.00 ± 0.02 . In contrast to the in vitro data, stereoselective

metabolism was observed in vivo for both transdermal and oral oxybutynin. Because the R isomer possesses greater receptor affinity and N-DEO is thought to play an important role in anticholinergic side effects, the distinct differences in metabolite concentrations following both transdermal and oral administration support the possibility of improved tolerability and comparable efficacy with the transdermal delivery system. In a crossover study by Appell et al. (30), pharmacokinetic parameters and saliva output were assessed following both transdermal and extended-release oxybutynin (OXY ER) administration. Steady state plasma concentrations were attained following the first transdermal application and second ER oral tablet. Stereoselective metabolism was observed for both the R- and S- isomers of OXY and N-DEO that paralleled data previously reported (26).

Saliva output has been shown in previous studies to be a valid surrogate marker of dry mouth (31,32). Saliva output was greater in patients receiving transdermal therapy when compared to extended release oral therapy. An inverse relationship was observed between N-DEO and saliva output, with lower levels of N-DEO correlating with greater total saliva weight, corresponding to the low incidence of dry mouth observed with administration of transdermal oxybutynin. A comparative review of the pharmacokinetic parameters of oxybutynin IR, oxybutynin ER, and oxybutynin TDS is provided in Table-2.

Table 2 – Comparative steady state pharmacokinetic parameters of oxybutynin immediate-release (IR), oxybutynin extended-release (ER), and oxybutynin transdermal (TDS).

Agent	Dosage	Mean C _{max} (ng/mL)	Mean AUC (ng·h/mL)	Mean T _{1/2} (h)	N-DEO / OXY	Ref.
Oxybutynin TDS	3.9mg qd Δ 3-4 d	6.6 (2.4)	408 (108)	7-8	1.3:1 (0.3)	25, 38
Oxybutynin IR	5 mg tid	12.4 (4.1)	81 (43)	9.0 (2.4)	5.5:1	25, 39
Oxybutynin ER	15 mg qd	6.7 (2.1)	109 (43)	13.8 (2.9)	4.1:1 (0.9)	30, 39

Standard deviation of the mean is in parenthesis; C_{max} = mean peak serum concentration; AUC = area under the curve; N-DEO = N-desethyloxybutynin; OXY = oxybutynin.

TRANSDERMAL OXYBUTYNYN CLINICAL RESULTS

The efficacy of OXY-TDS has been evaluated in several clinical trials. A short-term, multicenter, double blind, dose-titration study compared OXY-TDS to immediate release oxybutynin in patients with urinary urge incontinence (33). Seventy-six patients with detrusor overactivity who were currently responding to oxybutynin IR were randomized to transdermal (N = 38) and oral therapy (N = 38) following a 2-week washout phase. Outcome measures included daily incontinence episodes recorded on 3 day bladder diaries, side effects recorded utilizing an anticholinergic symptom questionnaire, and visual analog scale measuring urinary control. Dose titration was initiated at levels based on previous oxybutynin IR dose and adjusted according to side effect profile, with the goal to achieve the maximal tolerable dose. Average daily incontinence episodes decreased in both treatment groups compared to washout by 5, ($p < 0.0001$) with no significant difference observed based on type of therapy (OXY-TDS from 7.2 to 2.4 and oxybutynin IR from 7.2 to 2.6; $p = 0.39$). Side effects were measured utilizing a non-validated anticholinergic symptom questionnaire and were rated as mild, tolerable, and intolerable. Dry mouth was rated as absent, mild, tolerable, and intolerable in 62%, 27%, 11% and 0% of patients treated with OXY-TDS. The corresponding values for patients treated with oxybutynin IR were 6%, 26%, 59% and 9%. Constipation was observed in 21% of patients in the transdermal group and 50% of patients in the oral group. In general, other side effects were described by fewer patients with less variance between the 2 treatment cohorts and included somnolence, dizziness, blurred vision, and impaired urination. Adverse effects unique to transdermal drug delivery systems included erythema at the patch application site with both active and placebo patches. Mild, moderate, and severe erythema was observed in 18%, 4%, and 1% of placebo patches and in 30%, 7%, and 1% of active therapy patches.

In another multi-center, double blind study, 520 patients with urge and mixed urinary incontinence

were randomized to receive 3 doses of OXY-TDS (1.3 mg/d, 2.6 mg/d, or 3.9 mg/d) or placebo, followed by a 12-week open-label, dose titration period to further evaluate efficacy and safety. Doses of 3.9 mg/d OXY-TDS led to a significant improvement in number of incontinence episodes/week (median change -19 vs. -14.5; $p = 0.0165$), mean daily frequency (mean change -2.3 vs. -1.7; $p = 0.0457$), average voided volume (median increase of 24 cc vs. 6 cc; $p = 0.0063$), and quality of life as measured by the total score on the Incontinence Impact Questionnaire (39% improvement vs. 28%; $p = 0.0327$) compared to placebo treatment. Doses of 2.6 mg/d significantly improved average voided volume (19 mL; $p = .0157$), however there were no other significant differences between the 1.3 mg and 2.6 mg groups compared to placebo treatment.

Safety was evaluated in all patients who participated in the double-blind study (N = 520), as well as the 12-week, open-label, dose titration period (N = 411). Application site skin reactions were the most commonly observed adverse events related to treatment, with the vast majority being mild to moderate in intensity. Erythema was observed in 3.1%, 4.5%, and 5.6% with 1.3, 2.6, and 3.9 mg/d transdermal oxybutynin compared to 2.3% with placebo. Pruritis was observed in 10.8%, 13.5%, and 16.8% of patients receiving active treatment compared to 6.1% with placebo. Withdrawal from the study was most commonly related to skin reactions and was seen in 10.2% of patients in the double blind period and 7.3% of patients during the dose titration period. Dry mouth was the most common anticholinergic side effect reported in the study and incidence did not differ between OXY-TDS and placebo (7% vs. 8.3%; $p = ns$). Other anticholinergic side-effects occurred infrequently and did not differ from placebo. The comparative efficacy and safety of transdermal oxybutynin, oral tolterodine and placebo were assessed in another double-blind, multi-center study (34). Three-hundred and sixty-one responders to previous pharmacotherapy were randomized to transdermal oxybutynin (3.9 mg/d, twice weekly), extended release tolterodine (4 mg daily), or placebo following a 2-week washout period. Patients were evaluated with regard to urinary symptoms based on

voiding diaries, incontinence-specific quality of life, and tolerability/safety. Patients treated with OXY-TDS achieved statistically significant reductions in daily incontinence episodes (-3 vs. -2; $p = 0.0137$), increased average voided volume (24 cc vs. 5.5 cc; $p = 0.001$), and improved quality of life (Incontinence Impact Questionnaire, $p = 0.0018$ and Urogenital Distress Inventory, $p = 0.0156$). Tolterodine ER also improved measured outcomes in a statistically significant fashion compared to placebo treatment. Active treatment resulted in a 75% reduction in daily incontinence episodes for OXY-TDS and tolterodine ER compared to a 50% reduction with placebo (both $p < 0.05$ vs. placebo). One-hundred and twenty patients were continent upon completion of the study, including 47 (39%), 47 (38%), and 26 (22%) patients receiving OXY-TDS, tolterodine ER, and placebo (both $p = 0.014$ vs. placebo). There were no significant differences in any evaluated outcome parameters between the 2 active treatment arms of the study.

Systemic adverse events occurred more frequently with tolterodine ER (23.6%) compared to OXY-TDS (19%) and placebo (12%). The vast majority of these were classified as mild and moderate. Dry mouth occurred in 4.1% of patients receiving OXY-TDS and 7.3% of patients receiving tolterodine ER compared to 1.7% with placebo (TDS, $p = 0.2678$; tolterodine ER, $p = 0.0379$). Constipation occurred in 3.3% and 5.7% of OXY-TDS and tolterodine ER treated patients, respectively. Application site skin reactions were the most common adverse events observed with transdermal oxybutynin therapy, and included pruritis (14% with transdermal vs. 4.3% with placebo) and erythema (8.3% with transdermal vs. 1.7 with placebo). Twenty-six of the 32 dermatologic adverse effects were rated by patients as mild or moderate. Twelve patients discontinued treatment in the OXY-TDS group as a result of skin site reactions, while 2 patients withdrew due to tolterodine ER related side effects.

Another study pooled data analysis from the 2 double-blind, phase 3 trials to better determine the safety and efficacy of OXY-TDS (35). The 241 patients that received 3.9 mg/d transdermal oxybutynin and 244 patients that received placebo treatment were included in the data analysis. Results

from the study showed statistically significant improvements in daily incontinence episodes, daily urinary frequency, urinary voided volume, and quality of life scores. Adverse events determined to be related to therapy occurred in 100 (41.3%) and 61 (24.9%) patients receiving active treatment compared to placebo. The benefit of placebo therapy in overactive bladder clinical trials has been well established. The observed improvements in patients treated with placebo in various clinical trials have been attributed to behavioral therapies (36). Patients in the current study were instructed to maintain normal fluid intake and continue with all nonpharmacologic modalities (e.g., timed voiding and pelvic floor muscle exercises). Another unique aspect of the study was the difference in clinical inclusion criteria used for study enrollment. Eighty percent of study 1 (37) participants reported no history of previous treatment with anticholinergic medications while 100% of study 2 (34) participants were known responders to anticholinergic therapy. Despite these different populations, efficacy of OXY-TDS was similar with respect to measured outcome parameters.

TRANSDERMAL OXYBUTYNIN SUMMARY

Transdermal oxybutynin has shown comparable efficacy and improved tolerability when compared to conventional pharmacotherapy. Systemic anticholinergic adverse effects are comparable to placebo, most likely due to avoidance of first pass hepatic metabolism and conversion of oxybutynin to N-desethyloxybutynin. OXY-TDS has predictable pharmacokinetic absorption and elimination parameters as shown in both in vitro and in vivo studies. Consistent plasma concentrations of oxybutynin avoid labile peak and trough concentrations seen with IR formulations, paralleling ER drug delivery. This novel drug delivery system has unique dermatologic skin application site reactions, including erythema and pruritis. Skin reactions are usually mild in severity and can be minimized by varying the site of patch application.

Most eczematous dermatologic reactions can be appropriately treated with a moderately potent topical corticosteroid cream. In conclusion, transdermal oxybutynin is an excellent treatment option for patients who find the side effects of oral antimuscarinics intolerable, as well as those patients who do not wish to administer their medication on a daily basis.

CONFLICT OF INTEREST

Doctor G. Willy Davila is consultant to Watson, the manufacturer of the transdermal oxybutynin patch.

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Correspondence address:

Dr. G. Willy Davila
Cleveland Clinic Florida,
Section of Urogynecology
2950 Cleveland Clinic Boulevard
Weston, Florida, 33331, USA
Fax: + 1 954 659-5587
E-mail: davilag@ccf.org

Retroperitoneoscopic Nephrectomy in Benign Pathology

Rodrigo S. Quintela, Leonardo R. Cotta, Marcelo F. Neves, David L. Abelha Jr, Jose E. Tavora

Section of Urology, Hospital da Previdência dos Servidores do Estado, Belo Horizonte, Minas Gerais, Brazil

ABSTRACT

Introduction: We report our experience with 43 retroperitoneal laparoscopic nephrectomy for benign kidney disease.

Materials and Methods: All patients had a poor function from obstructive uropathy and renal atrophy. None of these patients had a previous lumbody. Retroperitoneoscopy was performed with 4 trocar port technique in a lateral position. The retroperitoneal space is created by using a Gaur's balloon made of sterile glove. The approach to vascular pedicle was done posteriorly and vessels were clipped by metal and Hem-o-lock (Weck Closure Systems, North Carolina, USA) clips. The sample was intact extracted in an Endo-Bag prolonging one trocar incision.

Results: Median operative time was 160 minutes and median blood loss was 200 mL. Four cases (9%) were converted to open surgery: one case due to bleeding and 3 cases due to technical difficulties regarding perirenal adherences. Most patients (39) checked out from the Hospital in day two. Four of them were left over 3 days due to wound complications.

Conclusions: Retroperitoneoscopy offers a safe, effective and reproductive access to nephrectomy for benign pathologies.

Key words: kidney; nephrectomy; laparoscopy; retroperitoneal space

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INTRODUCTION

Laparoscopic nephrectomy was first successfully performed by Clayman in 1990 using the transperitoneal route (1). The pure retroperitoneal access for nephrectomy was described by Gaur three years later, using a balloon to create the surgical working space (2,3). Despite the preference for retroperitoneal approach in open urologic surgery worldwide the transperitoneal approach is the preferred technique for laparoscopic urologic surgery. Furthermore direct retroperitoneal access (retroperitoneoscopy) is attracting more interest and application in urology, becoming the preferential approach for nephrectomy in many expertise laparoscopic centers (4-9). This data de-

scribes our experience with retroperitoneoscopic simple nephrectomy.

MATERIALS AND METHODS

Forty-three retroperitoneal laparoscopy nephrectomies were performed from November 2003 through 2005 for benign kidney disease. Our initial experience started with retroperitoneal approach. This data show patients aged between 25-75 years, mean age was 47 years being 15 male and 28 females. Twenty nephrectomies (46%) were performed in right kidneys and 23 cases in the left kidney (54%). Symptomatology was presented as lumbar pain (56%),

pyelonephritis in 16 cases (37%) and three cases (7%) with renovascular hypertension. The work up was done in all cases following ultrasound, intravenous pyelogram (IVP) or axial computerized tomography and scint scan. Thirty-three patients (76%) presented hydronephrosis with no renal function and the other 10 patients (24%) presented renal atrophy. The etiology of the renal damage is showed in the Table-1. Three of the patients presented horseshoe kidneys with UPJ (ureteral pelvic junction) syndrome. Two patients had previous lumbar urologic interventions (percutaneous nephrolithotripsy and a percutaneous nephrostomy).

Surgical Technique

The patient is placed in lateral position as in an open surgery (classical lumbotomy position) with general anesthesia. In an attempt to get more room to face up the kidney, we flexed the table. The camera assistant stays at the surgeon’s side at a cephalic position and the second assistant stays at the opposite side. A transverse incision (15 mm) is made just below the 12th costal arc and the muscles are dissected until the toracolumbar fascia is opened achieving the retroperitoneal space. A digital dissection is made in the retroperitoneal space pulling the peritoneum anteriorly and displacing the fat from this body wall. A Gaur balloon (Figure-1) is placed in the space and filled with 800 mL of saline solution. The Hasson trocar is placed and fixed at the body wall to avoid air linkage. A CO₂ insufflation is performed at a pressure of 12 mm. A 0° laparoscopic lens is introduced

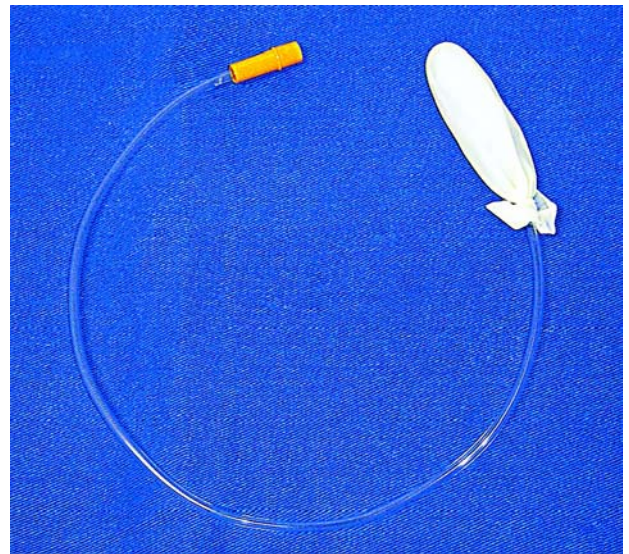


Figure 1 – Gaur’s balloon made of a Nelaton 16F catheter and a finger glove.

by the Hasson port and the other trocars are placed under direct vision: a 10 mm trocar is placed 2 cm above the iliac crest and two 5 mm trocars are placed in anterior axillary line (one next to the costal arc and the other by the iliac crest) (Figure-2).

The psoas muscle is the main anatomic landmark. This muscle is dissected and the ureter and the

Table 1 – Etiology of the lost renal function.

Pathology	Patients (%)
Ureteropelvic junction stricture	18 (42%)
Ureteral calculi	12 (27.7%)
Ureteral trauma	3 (7%)
Renal tuberculosis	3 (7%)
Congenital renal atrophy	3 (7%)
Renovascular hypertension	3 (7%)
Renal trauma	1 (2.3%)
Total	43 (100%)

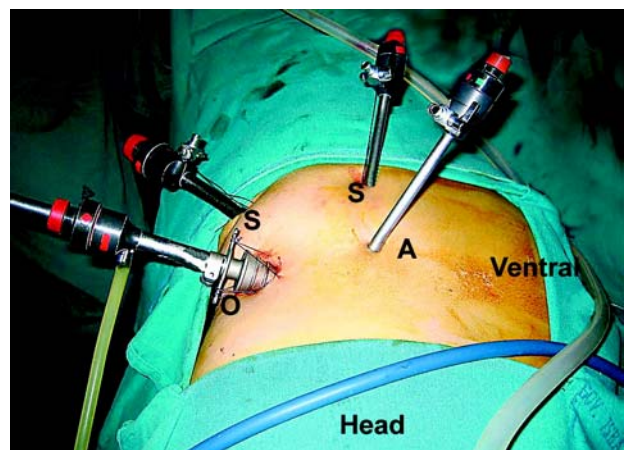


Figure 2 – Superior view of trocar port incisions for a left side retroperitoneoscopic nephrectomy. The Hasson trocar is fixed with sutures. The lens port (O), the surgeon ports (S) and the assistant port (A) are signaled.

gonad vein in the left or the inferior vena cava in the right are identified. The renal vein is dissected in the right side following the vena cava and the renal artery is dissected over the renal vein. In the left side, the renal vein is identified following the gonad vein and the artery is found just above the renal vein. Metal clips are used to occlude the artery and a Hem-o-lock® (Weck Closure Systems, North Caroline, USA) clip is used at the renal vein. After the vascular control, the dissection is initiated inside the Gerota's fascia by the renal upper pole preserving the adrenal gland in most of the cases. The lower pole then is dissected and the ureter is clip occluded with a metal clip. In cases of horseshoe kidney, the renal isthmus is coagulated with an electrocautery and laparoscopically sutured with absorbed suture if necessary. In voluminous hydronephrotic kidneys the fluid in the collecting system is aspirated to facilitate perirenal dissection. The specimen is entrapped in a handmade bag. In cases where the samples are small, we utilize the first 15 mm lumbar incision to remove the specimen and with larger samples we prolong the inguinal port incision making a small Gibson's incision (Figure-3). A Penrose drain is placed in cases of infected kidney.

RESULTS

All of the surgeries were performed by the same surgeon or under his supervision. Table-2 resumes the results. Median operative time was 160 minutes (120 to 240 minutes) with average estimated blood loss of 200 mL. Blood transfusion was not necessary in any of the cases. Three patients presented intra surgical bleeding during pedicle dissection. Two patients with renal vein bleeding were laparoscopic controlled with a Hem-o-lock clip close to the vena cava. Another bleeding from an injury at the right adrenal vein required conversion to open surgery.

There were no major complications. Six patients developed abdominal body wall complications: three patients developed subcutaneous emphysema with no clinical repercussion and a spontaneous resolution; two patients developed surgical wound hematoma in the first trocar incision and one patient



Figure 3 – Final aspect of the incisions. The specimen was removed by the 5 cm inguinal incision. A Penrose drain is left in the dorsal surgeon working port.

developed surgical wound infection. All of those patients were treated clinically.

Conversion was necessary in 4 cases (9%). One patient due to hemorrhage and three patients due to technical difficulties. All of them presented chronic or tuberculous pyelonephritis and perirenal adherence. In none of the cases surgical reintervention was needed.

Diet was initiated 6 hours after surgery. Most of the patients (39) were released from the hospital the second day after surgery. Four patients were left in the hospital for more than 48 hours due to surgical wound complications.

Histopathological diagnosis confirmed three cases of renal tuberculosis and 40 cases of renal atrophy with or without chronic inflammatory process.

Table 2 – Surgical results.

Patients	43
Operative time (median)	160 minutes
Blood lost	200 ml
Conversion (%)	4 (9%)
Major complication (%)	0
Minor complication (%)	6 (13%)
Hospital stay	2 days

COMMENTS

Laparoscopic nephrectomy is widely performed by the transperitoneal approach. After retroperitoneal technique description by Gaur these has become the preferential approach in outstanding centers for the surgical treatment of most kidney pathologies even renal tumors (4-9).

The advantage of retroperitoneoscopy are the preservation of the peritoneal cavity and the posterior access to the renal pedicle making possible a straight dissection and the control of the vessels in the first step of the surgery. This approach can be done without any difficulties even in hard cases (10,11).

The main disadvantage of retroperitoneoscopy is the reduced working space requiring a better synchronized surgical team to avoid instrument collision. The use of Gaur's balloon creates a large space, which allow the surgeon to get enough room reaching all the kidney limits.

The main contraindication of retroperitoneoscopy is the presence of previous lumbotomy. Relative contraindication because of technical aspects should be attempt in patients with chronic inflammatory pathologies such as renal tuberculosis or xantogranulomatous pyelonephrosis (10-12). In those cases, the possibility of conversion is higher because of the adherences. In 3 cases of this series, patients with a chronic inflammatory process (one with renal tuberculosis) were submitted to conversion to open surgery due to technical difficulties. Furthermore, in two patients with tuberculosis the surgery was performed without any difficulties or complications. Some reported series show a significant number of cases of renal tuberculosis successfully treated by retroperitoneoscopy (10,11). Although it presents a better chance of conversion, the presence of a chronic inflammatory process is not an absolute contraindication for laparoscopic nephrectomy. In such cases, transperitoneal or hand-assisted laparoscopy should be a better option.

Previous minimally invasive lumbar procedures such as nephrostomy and percutaneous nephrolithotripsy do not exclude retroperitoneoscopy (6,7,13). In two patients of this series with previous

history of nephrostomy and percutaneous nephrolithotripsy, the procedure was performed without any difficulties.

In patients with horseshoe kidney the presence of anomalous vessels require an extra careful vascular approach (3). In three patients of this series with horseshoe kidney retroperitoneal laparoscopic nephrectomy was performed without difficulties in reaching the renal pedicle but a longer operative time was needed.

The incidence of vascular lesions in transperitoneal urological laparoscopic surgery vary between 1.5% to 2% in large series (14,15). Although there is not much data for retroperitoneal approach its reported incidence is similar (16). In this data we had three cases of vascular bleeding during pedicle dissection. In one of the cases a left adrenal vein bleeding required conversion to open surgery. Conversion was not required in two other cases of renal pedicle bleeding. Conversion to open surgery depends on the extension of the vascular lesion and of the surgeon skills to control bleeding. A temporary increase of inflation pressure up to 15 or 20 mmHg reduces venous hemorrhage in the retroperitoneal space and a vascular control maneuver must be considered. In one case it was necessary the placement of another trocar port for a better exposition. We experienced no bleeding problems using metal clips for renal artery control and Hem-o-lock (Weck Closure Systems, North Caroline, USA) clips for renal vein control.

Emphysema is the most common abdominal wall complication added to hematoma and wound infection (17). Hematoma at the place of the trocar port is more often seen in retroperitoneal laparoscopy rather than in transperitoneal laparoscopy. The reason for that is the thick layer of lumbar muscle that offers a higher tension in mobilizing instruments. This problem can be reduced by choosing the right place for the trocar introduction in the body wall avoiding paravertebral muscle and a close proximity to the bone structure such as costal arc and iliac crest. In this data we had two cases of wound hematoma with a spontaneous resolution and one case of wound infection treated clinically. The use of a blunt tip cannula (Auto Suture-Menlo Park, California) not requiring fixation to the body wall with sutures can avoid this complication.

The CO₂ inflation can cause subcutaneous emphysema, especially pneumothorax and pneumomediastine if the retroperitoneal pressure reach levels over 15 mmHg (18). Usually no important clinical repercussion is seen on those patients (19). A pressure of 12 mmHg gives the surgeon a good working space. Three cases of subcutaneous emphysema with no clinical repercussion were observed in this data.

Total surgical conversion frequency was 9%. Most of those conversions occurred due to hemorrhage or technique difficulties caused by perirenal adherence. The data literature shows up to 10% of conversion for simple laparoscopic nephrectomy (6,9). The majority of conversions occur due to inflammatory processes or previous surgeries (11). When surgical conversion becomes necessary it can be rapidly performed by lumbotomy, prolonging the first trocar incision that allows the surgeon to continue with the conventional lumbar incision with good cosmetic results.

The sample extraction can be performed by a new incision, amplifying the trocar incision or with morcellation. Pfannenstiel incision, often propagated for transperitoneal laparoscopic nephrectomy, can be an alternative for sample extraction opening the peritoneum close to the upper abdominal wall at the end of the procedure. Morcellation avoids incision augmentation but promotes longer operative time and less accuracy for the histopathology (20). We usually extract all samples by the initial trocar incision if possible or by making a small 5 cm inguinal incision (Gibson's incision) with low morbidity and good cosmetic results.

The retroperitoneal approach offers a lower morbidity when compared to the transperitoneal approach because it does not violate the peritoneal cavity. This benefit occurs not only due to less intraperitoneal manipulation and less organ lesions but also due to the reduction of the peritoneal contact with urine and blood (5,7,13). Infected urine elimination during the surgery was observed in many patients in this series without any further complication such as infection or postoperative ileums.

Urology departments worldwide start their laparoscopic nephrectomy experience through

transperitoneal access, which is considered the safest one and also the one that facilitates laparoscopic dissection especially in early experiences. This series shows the initial experience using retroperitoneal approach in a public Brazilian medical center without any previous familiarity with urological laparoscopic surgery. This experience demonstrates that the retroperitoneal approach is a safe, reproductive and effective access for simple nephrectomy.

CONCLUSION

The laparoscopic retroperitoneal approach for simple nephrectomy is a challenge for the surgeon due to a smaller surgical working space but on the other hand it is benefic to patients because it does not violate the peritoneal cavity. Retroperitoneal and transperitoneal laparoscopic approaches have the same surgical indications but previous lumbotomy is a relative contraindication for retroperitoneal access. Minimally invasive lumbar procedures such as nephrostomy and percutaneous nephrolithotripsy are not contraindications.

An advantage to retroperitoneoscopy is the straight access to the kidney and its renal pedicle making possible an easier and faster approach as well as vascular control. Disadvantages include the need to create a retroperitoneal space and a small working area to dissect, proceed reconstructive maneuvers and bag the sample to extract it out of the body.

Retroperitoneoscopy must be considered a safe, effective and reproductive surgical technique for nephrectomy in benign renal diseases.

CONFLICT OF INTEREST

None declared.

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Correspondence address:

Dr. Rodrigo Silva Quintela
Rua Correias 281 / 201
Belo Horizonte, MG, 30315-340, Brazil
E-mail: quintelarod@yahoo.com

EDITORIAL COMMENT

It is a paper describing a retroperitoneal approach for nephrectomy in benign disease. Endoscopic nephrectomy is usually performed by transperitoneal rout and the merit of the paper is that it underlies the advantages of using a retroperitoneal approach and shows that it is feasible. One important shortcoming is the absence of a control group.

I believe that vessels should be ligated with a transfixational technique since it reduces the risk of intra and postoperative bleeding.

Conversion rate was fairly high. Manual dissection of the peritoneum gives a large working space. A hand-assisted technique also makes the operation easier, quicker and safer.

It could be argued that the total length of all incisions is longer than a small anterior extraperitoneal incision or dorsal incision for open surgery. The advantage with an endoscopic approach would be an extraction sit with low morbidity and good cosmetic results. A Pfannenstiel incision is therefore often propagated for the extraction (can also be used for a hand assisted procedure).

Dr. Jonas Wadström

*Department of Surgical Sciences
Uppsala University Hospital
Uppsala, Sweden*

E-mail: jonaswadstrom@akademiska.se

EDITORIAL COMMENT

Nowadays many authors in many countries including Japan have already described retroperitoneal nephrectomy for renal disease as a standard care. From this standpoint of view, the impact and origi-

nality of this manuscript is low internationally. However, as this may be a progressive approach in developing countries, this manuscript will be informative for many urologists working in these countries.

Dr. K. Mita

*Hiroshima University, Dept of Urology
Graduate School of Medical Sciences
Hiroshima City, Japan
E-mail: mita@plum.ocn.ne.jp*

EDITORIAL COMMENT

The authors are to be congratulated on their excellent clinical results with retroperitoneoscopic nephrectomy.

In cases with giant hydronephrosis, I usually insert percutaneous nephrostomy intraoperatively and adjust the volume of fluid within the collecting

system to facilitate perirenal dissection in the retroperitoneal space.

In cases with horseshoe kidney, additional renal arteries may arise from the aorta or the iliac vessels. Using the retroperitoneal approach, it might be difficult to control hemorrhage or dividing the renal isthmus, especially when it is thick. Therefore, I prefer to use the transperitoneal approach in such cases.

Aside from early and straightforward access to the renal vessels, the retroperitoneal approach is not an easy operation because of a narrow working space and the relative paucity of anatomical landmarks. Although the authors successfully performed retroperitoneal nephrectomy despite of no previous experience with urologic laparoscopy, I think it is exceptional and inapplicable to general urologists. Educational training of laparoscopic surgery is desirable.

Dr. A. Terai

*Department of Urology
Kurashiki Central Hospital
Kurashiki, Japan*

E-mail: at7899@kchnet.org.jp

EDITORIAL COMMENT

This is a retrospective review of a clinical experience with retroperitoneal laparoscopy for benign kidneys at a public hospital. The authors adequately describe their technique. The results are in general favorable, but there were several open con-

versions. Mostly for failure to progress from adhesions but there was at least one case of bleeding required open conversion. Complications were reported and discussed. I agree with the author's contention that the retroperitoneal technique is underutilized.

Dr. David A. Goldfarb

*Division of Renal Transplant
Cleveland Clinic Foundation
Cleveland, Ohio, USA*

E-mail: goldfad@ccf.org

Orthotopic Ileal Neobladder Reconstruction for Bladder Cancer: Is Adjuvant Chemotherapy Safe?

Murugesan Manoharan, Martha A. Reyes, Rakesh Singal, Bruce R. Kava, Alan M. Nieder, Mark S. Soloway

Department of Urology and Department of Medicine (RS), University of Miami School of Medicine, Miami, Florida, USA

ABSTRACT

Objective: We examined our database of patients undergoing radical cystectomy (RC) with orthotopic neobladder (NB) to determine whether adjuvant chemotherapy in this group is safe.

Materials and Methods: We performed a retrospective analysis of patients who underwent radical cystectomy and urinary diversion between 1992 and 2004. Relevant clinical and therapeutic data were entered into a database. High-risk bladder cancer patients who underwent NB were identified. They were stratified into 2 groups, those who received adjuvant chemotherapy and those who did not. The incidence of complications between the 2 groups was analyzed and compared.

Results: Over the 12-year period, 136 patients underwent RC and NB construction for bladder cancer. Of these, 83 patients were at high risk for recurrence. Nineteen patients received adjuvant chemotherapy and 64 did not. The complication rate in the adjuvant chemotherapy group was 53% and it was 23% in those who did not receive chemotherapy. There were no perioperative or treatment related death. There were 2 patients with grade 4 toxicity in the adjuvant chemotherapy group. There was a statistical difference between these two groups with regard to the incidence of complications. However, none of these complications was life-threatening, required only conservative treatment and caused no long-term disability.

Conclusions: Adjuvant chemotherapy is a safe treatment for patients undergoing RC and NB substitution. Hence, the option of orthotopic NB should not be denied in selected bladder cancer patients with high risk for recurrent disease.

Key words: bladder neoplasms; urinary diversion; chemotherapy

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INTRODUCTION

38,000 men and 15,000 women are newly diagnosed with bladder cancer annually in the United States and about 15000 are expected to die from this each year (1). A common therapeutic modality for treating muscle invasive bladder cancer is radical cystectomy (RC) with the reconstruction of a urinary diversion. Over the last 15 years, orthotopic neobladder

(NB) reconstruction has become a recognized method of urinary diversion in properly selected bladder cancer patients as the NB offers quality of life advantages with no significant difference in morbidity in relation to other types of urinary diversion such as ileal conduit (2-4). Other advantages of a neobladder include the achievement of a low-pressure reservoir, maintenance of near-normal volitional voiding and the avoidance of an external stoma.

Currently patients at high risk for recurrent disease, such as clinical stage > T2 with or without positive lymph nodes are frequently offered adjuvant chemotherapy (AC). Studies have demonstrated that AC in these situations have a positive clinical impact and improves survival (5-7). Even in these high-risk patients, NB reconstruction is increasingly being offered as a method of choice for urinary diversion. The incidence of urinary tract infections, the need for intermittent self-catheterization, incomplete emptying of bladder and mucus plugs are common problems associated with a NB reconstruction. Chemotherapy is associated with significant toxicity such as neutropenia and immunosuppression resulting in increased incidence of complications including sepsis (8). Consequently, concern arises whether the NB patients can tolerate the AC safely.

There are unanswered questions about the complication rate related to adjuvant chemotherapy in a NB setting. There is paucity of information in the current literature regarding the incidence of complications in patients with a NB who received AC compared to those who did not receive AC. Hence, we analyzed two groups of our NB patients, those who received adjuvant chemotherapy and those who did not, comparing the complications to determine whether adjuvant chemotherapy is safe in patients undergoing RC with NB.

MATERIALS AND METHODS

A retrospective analysis was performed on patients with bladder cancer treated with radical cystectomy and neobladder reconstruction between 1992 and 2004 at the University of Miami. After obtaining institutional review board approval, relevant clinical and therapeutic data were entered into a database. Following a standard radical cystectomy and pelvic lymph node dissection, a neobladder reconstruction was performed using modification of the technique described by Hautmann & Studer (9,10). Patients at high risk for recurrent disease following RC such as clinical stage > T2, nodal disease and/or metastatic disease were referred to the oncologist for considering adjuvant chemotherapy. The final

decision to administer AC was made by the oncologist in conjunction with the patient's desires.

The patients were stratified into 2 groups, those who received adjuvant chemotherapy and those who did not. Adjuvant chemotherapy protocols were administered at the discretion of the medical oncologist. The incidence of urinary tract infection, gastrointestinal and hematologic complications, wound infections and other complications between these 2 groups were analyzed and compared. The toxicity of chemotherapy in the group who received adjuvant chemotherapy was scored in accordance to the National Cancer Institute Common Toxicity Criteria (NCI CTC) and recorded in to the database. The chi-square test was used to assess statistical significance in complication rates between the groups, ($p \leq 0.05$ considered statistically significant).

RESULTS

Over a 12 year period, 136 patients underwent radical cystectomy and neobladder reconstruction for bladder cancer at our center. 129 (95%) were males and 7 (5%) were females with a mean age of 66 years. 83 (61%) patients were at high risk for recurrence and had clinical stage > T2, nodal disease and/or metastatic disease. In this group, 19 patients received adjuvant chemotherapy (Group-1) and 64 did not (Group-2). Table-1 shows the base line characteristics and the pathologic stage of the study groups. The distribution of chemotherapy regimens are detailed in Table-2. The complications are listed in Table-3 and toxicity by grade in group 1 is shown in Table-4.

Overall, 25 patients (29%) suffered a complication: 7 (29%) patients had urinary tract infections; 7 (21%) had gastrointestinal complications; 8 (33%) had hematologic manifestations; 2 (8%) had wound infection and 10 (12%) had miscellaneous complications. In miscellaneous complications one patient from Group-1 had to change chemotherapy regimens from gemcitabine and cisplatin to paclitaxel and carboplatin because of renal impairment; two patients had poor appetite and loss of weight. From Group-2, two patients had cardiac complications (severe chest pain with atrial fibrillation on

Table 1 – Base-line characteristics of the patients.

Characteristics	NB with AC Group 1	NB without AC Group 2
N. of patients	19	64
Sex (M/F)	17/2	62/2
Mean Age (years)	66	66
Mean Follow up (months)	34	29
Pathological Stage		
T2	6	30
T3	9	28
T4	4	6
N0	4	54
N1	5	4
N2	10	5
Nx	0	1
M0	18	62
M1	1	1
Mx	0	1

NB = neobladder; AC = adjuvant chemotherapy.

electrocardiogram, and myocardial infarction), two patients had wound dehiscence, one patient had pouchitis requiring intravenous antibiotics, one patient had an entero-neobladder fistula that required repair and one had a pelvic abscess that required CT guided drainage. Complications were demonstrated in 10 (53%) patients from Group-1 and 15 (23%) patients from Group-2 ($p < 0.01$). As expected, hematologic complications were the most frequent to occur in Group-1. Three patients had anemia, 3 patients had neutropenic fever, and 2 patients had

Table 3 – Complications.

	Group-1, N (%)	Group-2, N (%)	p Value
Urinary tract infection	2 (11)	5 (8)	0.70
Gastrointestinal	5 (26)	2 (3)	< 0.01
Hematologic	8 (42)	0	< 0.01
Wound infection	0 (0)	2 (3)	0.43
Others	3 (16)	7 (11)	0.56

Table 2 – Distribution of chemotherapy regimens in group-1.

Chemotherapy	N. of Patients
Methotrexate, vinblastine, doxorubicin & cisplatin (MVAC)	9
Paclitaxel & carboplatin	3
Gemcitabine & platinum	6
Carboplatin & etoposide	1
Total	19

anemia and neutropenic fever. Urinary tract infection was the most frequent complication in Group-2. There were no perioperative or treatment related deaths. Although the rate of hematologic complications in Group-1 was significant, these complications were not life-threatening, required only conservative treatment, and there were no long term sequelae. Additionally symptoms were transient and resolved when chemotherapy was completed.

Table 4 – Distribution of chemotherapy toxicity by grades according to the National Cancer Institute Common Toxicity Criteria.

Toxicity Type	Group 1 (n = 19) N (%)
Gastrointestinal	
Grade 1	4 (21)
Grade 2	1 (5)
Grade 3	0 (0)
Grade 4	0 (0)
Hematologic	
Grade 1	3 (16)
Grade 2	0 (0)
Grade 3	3 (16)
Grade 4	2 (11)
Other	
Grade 1	2 (11)
Grade 2	1 (5)
Grade 3	0 (0)
Grade 4	0 (0)

COMMENTS

In recent years, the neobladder has become the preferred form of bladder reconstruction in a selected patient population after radical cystectomy (2). The neobladder has replaced ileal conduit as the standard procedure due to better quality of life outcomes, avoidance of stoma, an improved body image and no additional morbidity (11,12). In addition, neobladder reconstruction does not compromise the cancer control.

Despite these advantages there are some disadvantages with the reconstruction of a neobladder. Some neobladder patients do not have the normal neuromuscular functions needed for micturition as voiding depends on a satisfactory relaxation of the pelvic floor and increase in the abdominal pressure. Therefore some patients with voiding dysfunction will require clean intermittent catheterization in order to empty the neobladder completely and to avoid urinary tract infections (13). During the immediate post operative weeks, patients are often required to catheterize to irrigate the bladder to remove the mucus.

Wood et al. (14) prospectively evaluated 66 patients with neobladder and found that 26 (39%) and 8 (12%) patients had a urinary tract infection and urosepsis, respectively. This study demonstrated that the estimated 5-year probability of urinary tract infection and urosepsis for patients who voided independently were 58% and 18%, respectively and that the only factors predictive of urinary tract infection on multivariate analysis were urine culture with greater than 100,000 cfu bacteria and female gender. Also, recurrent urinary tract infection was the only predictor for urosepsis and intermittent catheterization or hydronephrosis was not related to urinary tract infection or urosepsis.

Despite the improvements in postoperative care and surgical techniques, approximately 50% of patients who undergo cystectomy can expect disease recurrence, which may require adjuvant chemotherapy. Many studies have reported that adjuvant chemotherapy gives an improved disease-free survival over radical cystectomy alone for extravesical bladder cancer (15,16). Susuki et al. (17)

demonstrated in a retrospective study that adjuvant chemotherapy with methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) and methotrexate, epirubicin and cisplatin (MEC) has a positive impact on survival in patients with lymph node-positive disease. Freiha et al. (7) demonstrated that patients treated with cisplatin, methotrexate & vinblastine (CMV) had a higher survival compared to those patients who did not receive adjuvant chemotherapy.

Michael et al. (16) evaluated 35 patients retrospectively who received either cisplatin, methotrexate, and vinblastine (CMV) or methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) and found nine episodes of febrile neutropenia (one fatal) and six episodes of thromboembolism (one fatal). The authors cautioned that the use of adjuvant chemotherapy with CMV or MVAC might cause serious toxicity. Furthermore, Pectasides et al. (18) investigated the use of Cisplatin, epirubicin and docetaxel together in transitional cell urothelial cancer and found that 53.3% patients required one dose reduction and 16.7% patients required two dose reductions for a nadir AGC $\leq 500/\text{mm}^3$. There were also four episodes of febrile neutropenia and sepsis occurred and no patient had a dose reduction or treatment delay for any grade 3/4 toxicity or treatment delays due to myelotoxicity. Any non-hematological toxicity was mild and infrequent. They cautioned that the response rate and toxicity of the combination of epirubicin, docetaxel and cisplatin were comparable with the methotrexate, vinblastine, doxorubicin, cisplatin (M-VAC) regimen. Unfortunately, the complication rate and ultimately safety of adjuvant chemotherapy following RC and NB reconstruction, has not been well documented in the literature.

After considering the above studies, we decided to compare the incidence of urinary tract infection, hematologic complications, and other complications in a group of patients who received a NB and adjuvant chemotherapy and one in which patients who did not for the purpose of demonstrating whether adjuvant chemotherapy is safe for patients undergoing radical cystectomy with NB.

Hematologic complications were reported only in the group of patients who received adjuvant chemotherapy: two patients with anemia, 1 with night time fevers, 1 with anemia and neutropenic fever and 3 patients with neutropenic fever. Urinary tract infection was surprisingly higher in group-2 than group-1, but without statistically difference. For the overall complication rate, there was a statistical significant difference ($p = 0.015$) demonstrated in 53% patients who received adjuvant chemotherapy compared to 23% patients who did not received adjuvant chemotherapy.

Patients, who are treated for invasive bladder cancer following RC with NB, must be counseled about the toxicity of adjuvant chemotherapy, a critical component to the treatment plan. There are considerable side effects from chemotherapy, which vary, depending on the agents, dose used and the duration of treatment. Of concern always is inability of many patients to tolerate all courses of planned chemotherapy secondary to postoperative morbidity or drug side effects.

Because of the increased risk of complications, physicians may be hesitant about suggesting adjuvant chemotherapy in patients with neobladder who are at a high risk for recurrence. But the positive impact of adjuvant chemotherapy, long-term disease-free survival and the good clinical safety profile has been shown in many studies (6,15,19). Furthermore, all the complications demonstrated in this study were not life threatening, transient and resolved when chemotherapy was completed. In addition, the complications reported in our study were not specific to patients with an orthotopic neobladder. In fact, most of the complications were related to adjuvant chemotherapy and can occur in other types of diversion such as ileal conduit. Manoharan et al. (20) have demonstrated that the complication rates following AC are similar in patients with ileal conduit and neobladder. Therefore the option of orthotopic neobladder should not be denied in bladder cancer patients at high risk for recurrent disease.

The antineoplastic agent combinations that offer the least toxic side effects with the most survival benefit have evolved during the past decade (21). Currently, the approach towards adjuvant systemic

treatment has changed due to the development of more tolerable antineoplastic agents with similar efficacy. The introduction of gemcitabine, a nucleoside antimetabolite that inhibits DNA synthesis and the taxanes as chemotherapy treatment choices for bladder cancer is a promising development. Gemcitabine, as a single agent has shown an overall response rate of about 25%, with a complete response rate of 9%, with the combination of cisplatin has already demonstrated similar objective response and survival rates with less toxicity than M-VAC, in patients with metastatic bladder cancer (21,22). At our center MVAC regimen has been largely replaced by gemcitabine and cisplatin.

There are some limitations to the interpretation of this data. This is a nonrandomized and retrospective study. Although it was a retrospective study, the strength of our series is the number (84) of high risk patients operated on by a single surgeon in the same center over 12 years. Another limitation of the study is that adjuvant chemotherapy protocols were performed by different physicians and regimens were not standard. This reflects the advances in the chemotherapeutic drugs, which resulted in regimen changes with time.

CONCLUSIONS

There was an increased incidence of complications such as hematological effects found in patients who received adjuvant chemotherapy, compared to those with neobladder alone. However symptoms were non life threatening, transient and disappeared when chemotherapy was discontinued. Adjuvant chemotherapy in neobladder patients is safe. Hence the option of orthotopic neobladder reconstruction should not be unfairly denied for bladder cancer patients, at high risk for recurrent disease, who may require adjuvant chemotherapy.

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CONFLICT OF INTEREST

None declared.

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Correspondence address:

Dr. M. Manoharan
Department of Urology
Miller School of Medicine University of Miami
P.O. Box 016960 (M814)
Miami, Florida, 33101, USA
Fax: +1 305 243-4653
E-mail: mmanoharan@med.miami.edu

EDITORIAL COMMENT

A recent meta-analysis addressing the value of adjuvant chemotherapy in bladder cancer has shown an absolute benefit of 11% and 16% in the 5-year overall survival and disease free survival in favor of adjuvant chemotherapy respectively. Unfortunately, all randomized studies present serious methodological problems making these results less reliable (1).

Despite the retrospective design of the present study it brings the message that hematological side effects of chemotherapy are mild and tolerable.

Furthermore, in the present days with the advent of new drugs with less toxicity we can witness better tolerance of the patients.

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Dr. Marcos F. Dall'Oglio

Division of Urology

University of São Paulo, USP

São Paulo, SP, Brazil

E-mail: marcosdallogliouro@terra.com.br

A Fourteen-Year Review of Radical Cystectomy for Transitional Cell Carcinoma Demonstrating the Usefulness of the Concept of Lymph Node Density

Chi W. Cheng, Chi F. Ng, Chi K. Chan, Wai S. Wong, Pun E. Hui, Yim F. Wong

Department of Surgery and Department of Clinical Oncology, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong, China

ABSTRACT

Objective: We studied the long-term outcome of radical cystectomy for transitional cell carcinoma and evaluated prognostic factors for disease specific survival.

Materials and Methods: A retrospective review was carried out for all cystectomies performed for transitional cell carcinoma between 1989 and 2002. Disease specific survival was correlated to patient, pathological and operative factors as well as to adjuvant therapy.

Results: Of the 133 cystectomies included, 100 were male and 33 were female patients. The median age was 69 years (range 43 to 86). The median follow up was 20 months (range 0 to 158). With univariate analysis, pT stage, N stage, lymph node density, carcinoma in-situ, surgical margin and post-operative radiotherapy to distant metastasis were predictive of disease specific survival. On the other hand, with multivariate analysis, only pT stage, lymph node density and post-operative radiotherapy to distant metastasis were predictive of disease specific survival. Within the group of node positive disease, lymph node density also predicted disease specific survival with both univariate and multivariate analyses. Patients with lymph node density 20% or below showed better disease specific survival.

Conclusions: pT stage and lymph node density were found to be the most important predictive factors for disease specific survival after cystectomy in the Asian population.

Key words: bladder; carcinoma, transitional cell; cystectomy; lymph nodes

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INTRODUCTION

Radical cystectomy is the standard surgical treatment for muscle invasive bladder transitional cell carcinoma (TCC) and can achieve good long term results for organ confined disease. Patients with locally advanced or nodal disease may also benefit from the surgery (1-3). pT staging and N staging have been widely accepted as important prognostic factors.

Both the value and the extent of pelvic lymphadenectomy have been controversial. Lymph node density (LND), defined as the percentage of resected lymph nodes that were involved and calculated by the division of the number of lymph nodes involved by the number resected, has also been found to be a useful prognostic variable (4). A retrospective review of radical cystectomy was carried out to evaluate prognostic factors including the LND

to see if they were also applicable to the Asian population.

MATERIALS AND METHODS

Radical cystectomy performed in the Prince of Wales Hospital for TCC between 1989 and 2002 were reviewed. Cystectomy was preceded by bilateral pelvic lymphadenectomy with the two specimens sent separately and followed by either an ileal conduit or a continent diversion. The boundaries of the pelvic lymphadenectomy were the muscle pelvic side wall laterally, vesical fascia medially, lateral border of external iliac vein superiorly, obturator nerve inferiorly, bifurcation of the common iliac artery proximally and femoral canal inferiorly.

Patients with bulky tumors might receive radical radiotherapy (RT) before salvage cystectomy. Younger patients with good renal function might receive neoadjuvant systemic chemotherapy before radical cystectomy at the discretion of the urologists. Patients with positive pelvic lymph nodes or minimal or positive surgical margins might receive post-operative RT to the pelvis. Patients with recurrence as distant metastases might receive post-operative systemic chemotherapy or post-operative RT to the metastases at the discretion of the oncologists.

Data were collected from patient case notes, patient or family telephone contact and electronic medical records, including patient (age, sex, mode of presentation), pathological (pT stage, N stage, number of nodes involved, number of nodes resected, LND, grading, coexistence of carcinoma in-situ or CIS, surgical margin) and operative factors (continent diversion, simultaneous nephrectomy, simultaneous urethrectomy) as well as adjuvant therapy (RT, chemotherapy). The staging system employed was the 2002 American Joint Committee on Cancer TNM staging system. In cases of mixed stages or grades, the highest stage or grade was documented. Presentation mode could either be progression from superficial disease or de novo muscle invasive. LND was defined as stated above. A positive surgical margin means a positive one confirmed microscopically and a minimal margin dictates that

cancer cells are found 1 mm or less close to the surgical margin.

End points recorded included recurrence and death. The time to first recurrence, the survival and the cause of death were documented. Recurrence free interval and patient survival were defined as the time from cystectomy to the end point (recurrence, death or censored). In the analysis of disease specific survival, patients who died of TCC were classified as deaths.

The Kaplan-Meier method was used to calculate the survival curves. The log rank test and the Cox proportional hazards model were used for univariate and multivariate analyses respectively, to assess the influence on the survival curves by patient, pathological and operative factors as well as adjuvant therapy. Logistic regression was used to assess the influence on LND by pre-operative and intra-operative parameters.

RESULTS

Clinico-pathological Features

One hundred and forty four cystectomies were performed in the 14 year period. Eleven cases were excluded from this review because of histology other than TCC (seven cases of adenocarcinoma, one case of squamous cell carcinoma, one case of leiomyosarcoma and two cases of carcinosarcoma). There were 100 males and 33 females. The mean and median ages were 67.1 and 69 years (range 43 to 86), respectively.

The indications for radical cystectomy were mainly muscle invasive disease (123 cases) except one case of CIS resistant to treatment and nine cases of recurrent pT1 disease. The details of histological findings were shown in Table-1. Reconstruction was achieved by ileal conduit in 112 cases and continent diversion in 21 cases. Continent diversion performed included 19 ileal neobladders, one Indiana pouch and one right colonic pouch. Nine patients had a simultaneous nephrectomy (three cases for simultaneous upper tract TCC and six cases for non-functioning kidneys) and 25 patients had a simultaneous urethrectomy. Lymph node status was

Table 1 – Number of patients with different histological findings.

Mode of presentation	Progression from superficial	14
	De novo muscle invasion	109
pT stage	Non-muscle invasive at cystectomy	10
	CIS	1
	1	9
	2	14
	2a	25
	2b	16
	3a	17
	3b	25
	4a	22
	4b	4
	Missing data	0
N stage	N0	82
	N1	12
	N2	25
	N3	1
	Missing data	13
M stage	M0	132
	M1	1
	Missing data	0
Grading	G1	1
	G2	25
	G3	106
	Missing data	1
	CIS	19
	Nil	114
	Missing data	0
Lymph node density	0%	82
	20% or less	15
	Above 20%	22
	Missing data	14
Margin	Clear	105
	Minimal of 1 mm or less	18
	Positive	10
	Missing data	0

CIS = carcinoma in-situ.

unknown in thirteen patients, otherwise, thirty eight patients (38/120 = 31.7%) showed positive lymph nodes. The mean and median numbers of nodes resected for the whole series was 9.48 and eight, respectively (range 1 to 49) while the mean and median numbers of nodes involved was 0.93 and zero, respectively (range 0 to 13). On the other hand, the

mean and median numbers of nodes resected for node positive cases was 9.62 and seven, respectively (range 1 to 49) while the mean and median numbers of nodes involved was 2.95 and two, respectively (range 1 to 13). In patients free of nodal disease, the mean and median numbers of nodes resected were 9.65 and eight, respectively (range 1 to 33).

The distribution of various pathological subgroups was as follows: 7.5% were superficial lymph node negative, 35% were muscle invasive lymph node negative, 25.8% were extravesical lymph node negative and 31.7% were lymph node positive disease. Moreover, the incidence of nodal involvement in various pT stages was found to be 11.1% in pT1, 16.0% in pT2, 43.6% in T3 and 57.1% in T4.

The number of cases that received RT and chemotherapy are shown in Table-2.

Table 2 – Number of patients with radiotherapy or chemotherapy.

Preoperative radiotherapy to bladder	5
Postoperative radiotherapy to pelvis	12
Postoperative radiotherapy to distant metastasis	21
Preoperative chemotherapy	16
Postoperative chemotherapy	5

Endpoints

Sixty one cases recurred at a median surveillance of 15 months (range 0 to 158). The median time to recurrence was nine months (range 0 to 67). Four cases recurred locally while the remaining 57 recurred as distant metastases.

Eighty four cases died being 68 of cancer at a median follow up of 20 months (range 0 to 158). Five cases of perioperative mortality (5/133 = 3.8%) within 30 days of cystectomy were also classified as cancer, as they died as a result of a procedure for the disease. The median time to cancer death was 13.5 months (range 0 to 118).

The 1,3,5 and 10-year overall survival were 69.5%, 47.4%, 37.2% and 25.2%, while the corresponding disease specific survival were 74.1%, 53.7%, 42.2% and 34.6%. The corresponding survival curves were shown in Figure-1.

The 5 and 10-year disease specific survival for various pathological subgroups were as follows:

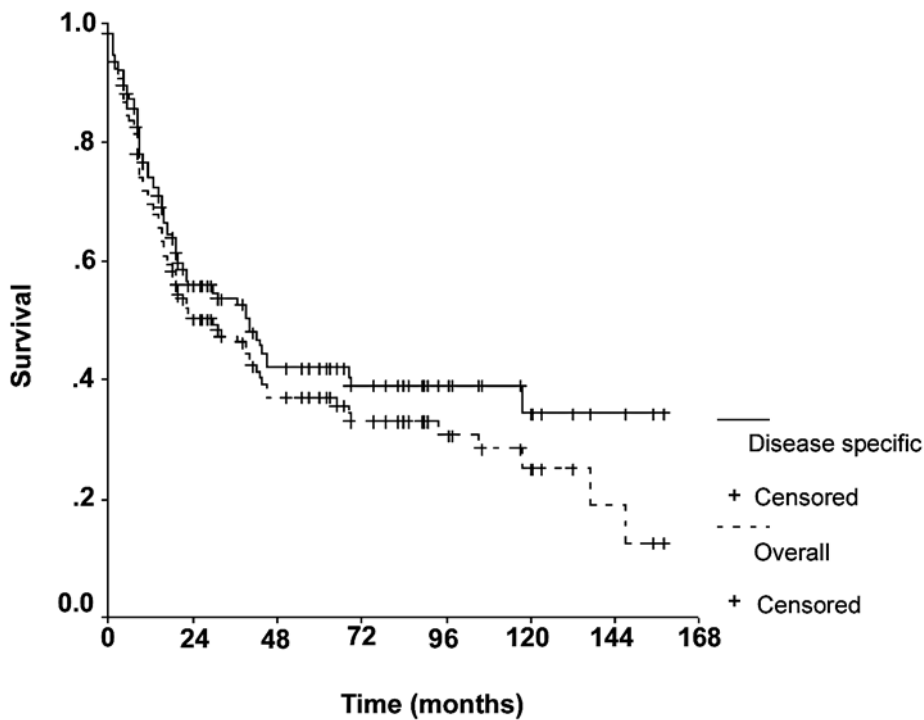


Figure 1 – Overall and disease specific survival curves.

Table 3 – Summary of univariate and multivariate analyses of effects of various prognostic factors on disease specific survival.

		Log Rank	Cox Regression
Patient factors	Sex	0.4308	0.748
	Age		0.193
	Presentation	0.5542	0.936
Pathological factors	pT stage	< 0.0001*	0.003*
	N stage	0.0003*	0.847
	Nodes involved		0.838
	Nodes resected		0.276
	LND	< 0.0001*	< 0.001*
	Grading	0.2912	0.328
	CIS	0.0417*	0.987
Operative factors	Margin	< 0.0001*	0.147
	Continent diversion	0.5009	0.997
	Nephrectomy	0.1502	0.588
	Urethrectomy	0.5158	0.939
Adjuvant therapy	Preoperative chemotherapy	0.2308	0.826
	Preoperative RT	0.5135	0.965
	Postoperative chemotherapy	0.2894	0.236
	Postoperative RT to pelvis	0.0703	0.381
	Postoperative RT to metastasis	0.0001*	0.011*

RT = radiotherapy; * = statistically significant.

71.4% and 35.7% for superficial lymph node negative, 72.7% and 61.5% for muscle invasive lymph node negative, 19.9% and 19.9% for extravesical lymph node negative and 28.7% and 28.7% for lymph node positive disease.

Prognostic Factors

With univariate analysis, pT staging, N staging, LND, CIS, surgical margin and post-operative RT to distant metastasis were predictive of disease specific survival. With multivariate analysis, only pT staging, LND and post-operative RT to distant metastasis were predictive of disease specific survival.

The disease specific survival curves defined by those factors predictive of disease specific survival were shown from Figures-2 to 7. The results of univariate and multivariate analyses on disease specific survival for all factors were summarized in Table-3. The disease specific survival curves for various pT stages were shown in Figure-2. The 5-

year survival for pT1, pT2, pT3 and pT4 disease were 71.4%, 69.1%, 17.2% and 12.2%, respectively (log rank, $p < 0.0001$). The disease specific survival curves for various N stages were shown in Figure-3. The 5-year survival for N0, N1, N2, and N3 disease were 52.2%, 61.0%, 17.8% and 0%, respectively (log rank, $p = 0.0003$). Similarly to what had been previously reported in literature, we also found a division line on LND at 20% discriminated patients into two groups with respect to disease specific survival (log rank, $p < 0.0001$). The disease specific survival curves for LND of 20% or less and LND more than 20% were shown in Figure-4. 54.0% of patients with LND of 20% or less survived five years or more, whereas all patients with LND more than 20% were either dead or censored at 39 months. The disease specific survival by surgical margin was shown in Figure-5. The 5-year disease specific survival for a clear, minimal or positive margin was 52.3%, 8.3% and 0% respectively (log rank, $p < 0.0001$). The disease

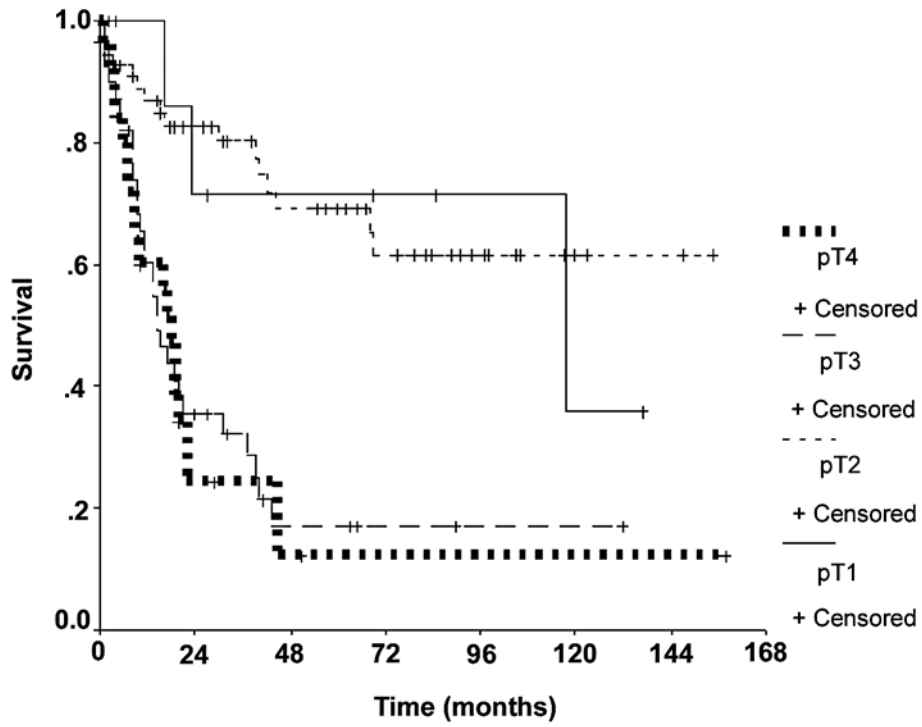


Figure 2 – Disease specific survival by pT stage.

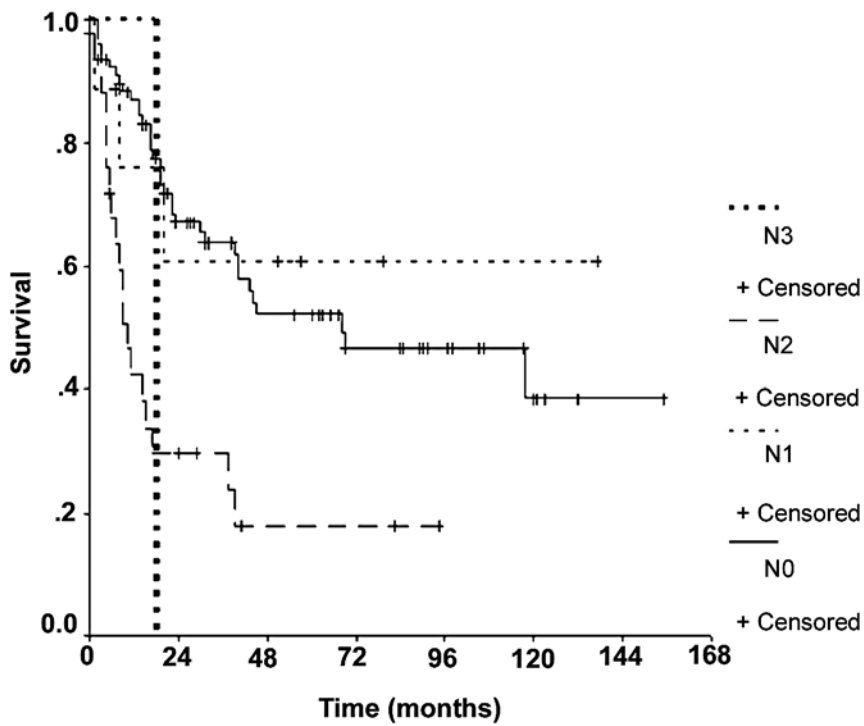


Figure 3 – Disease specific survival by N stage.

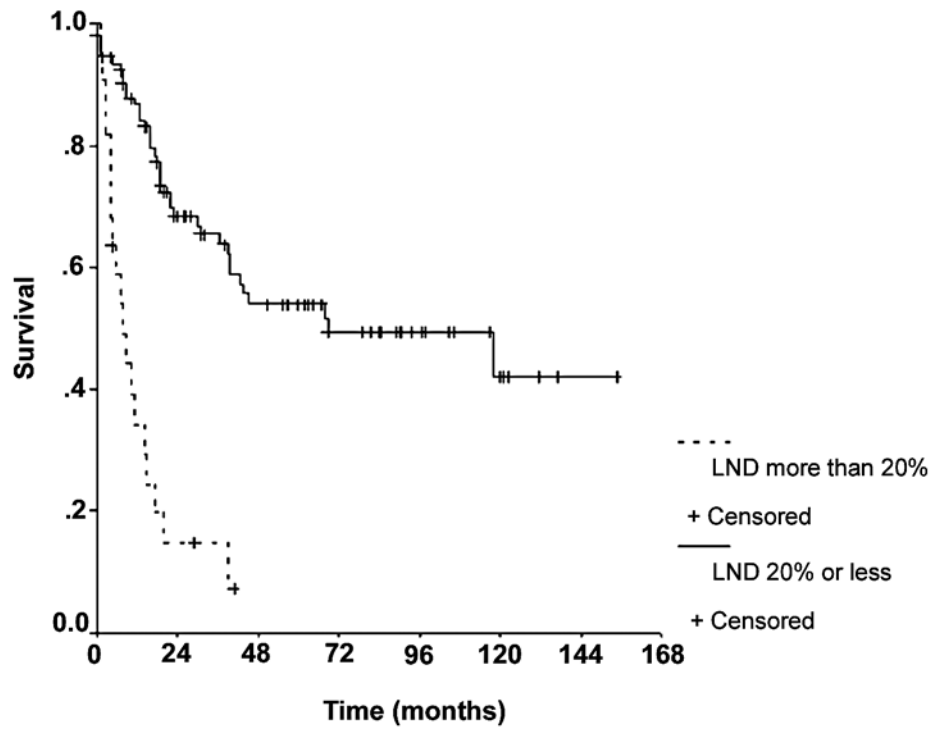


Figure 4 – Disease specific survival by lymph node density.

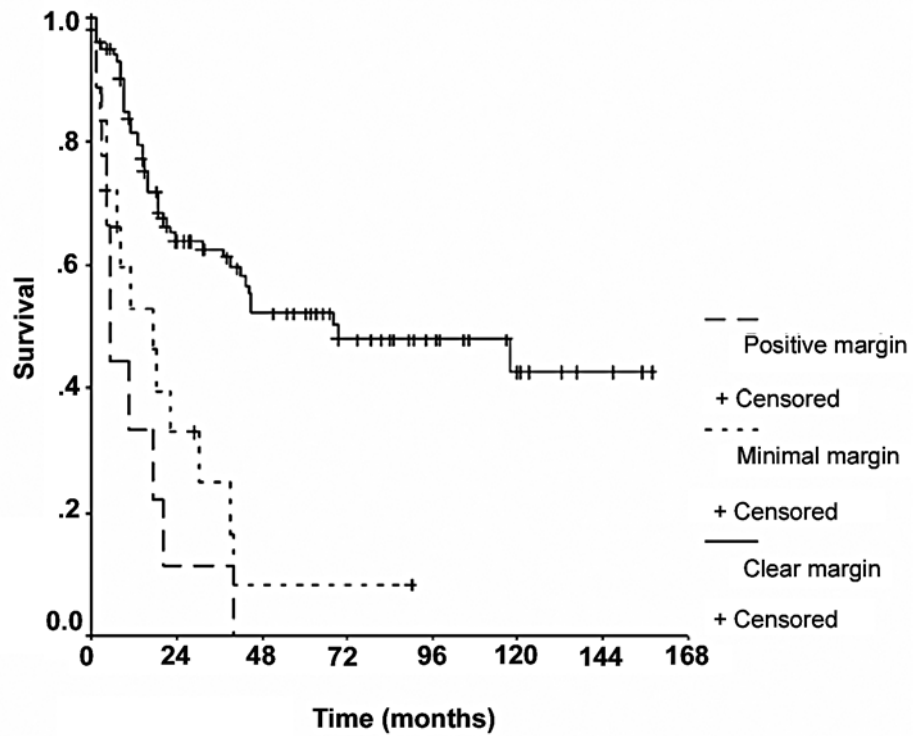


Figure 5 – Disease specific survival by surgical margin.

specific survival by presence or absence of CIS was shown in Figure-6. The 5-year disease specific survival was 37.9% without CIS and 64.9% with CIS (log rank, $p = 0.0417$). The disease specific survival by post-operative RT to distant metastasis was shown in Figure-7. The 5-year disease specific survival was 51.9% without post-operative RT to distant metastasis and 0% with post-operative RT to distant metastasis (log rank, $p = 0.0001$).

Within the group of node positive disease, we also found a division line on LND at 20% discriminated patients into two groups with respect to disease specific survival (log rank, $p = 0.0003$). LND of 20% predicted disease specific survival with both univariate and multivariate analyses. The disease specific survival curves for LND of 20% or less and LND more than 20% in patients with nodal disease were shown in Figure-8. 64.3% of patients with LND of 20% or less survived five years or more, whereas all patients with LND more than 20% were either dead

or censored at 39 months. Furthermore, in this group of node positive patients, neither the pT stage nor the number of nodes involved or resected, affected the disease specific survival in multivariate analysis.

We also analyzed by logistic regression the effects on LND (cut off point at 20%) by pre-operative and intra-operative factors to see if LND could be predicted before proceeding with cystectomy. These factors included sex, age, presentation mode, pT stage, grading, CIS, number of nodes resected, pre-operative RT, pre-operative chemotherapy, continent diversion, simultaneous nephrectomy and simultaneous urethrectomy. However, no such factor was found to predict LND in our series.

COMMENTS

This is a retrospective review with a relatively small sample size and short follow up period than

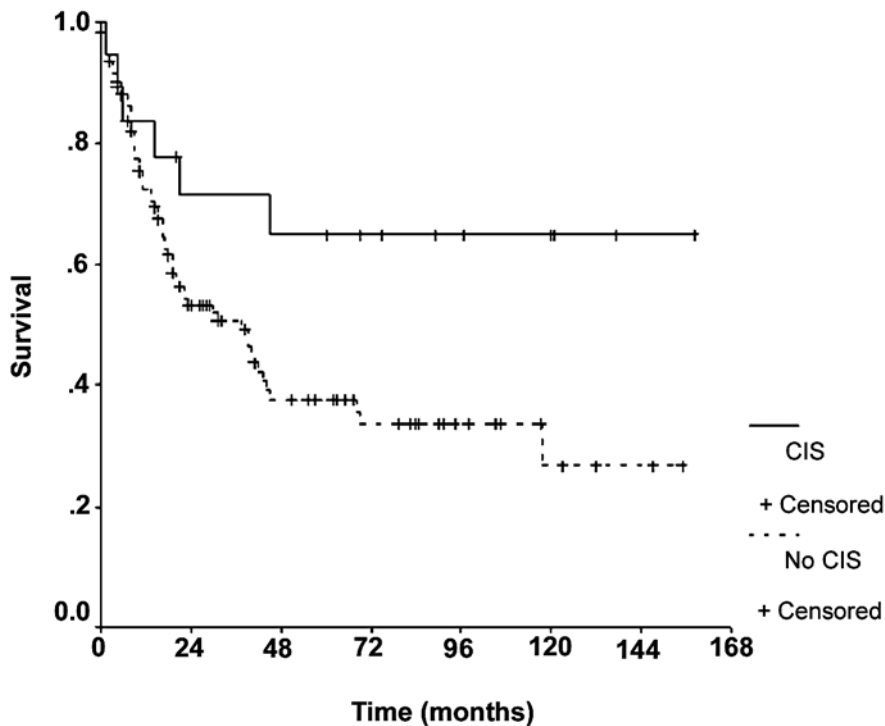


Figure 6 – Disease specific survival by presence of carcinoma in-situ.

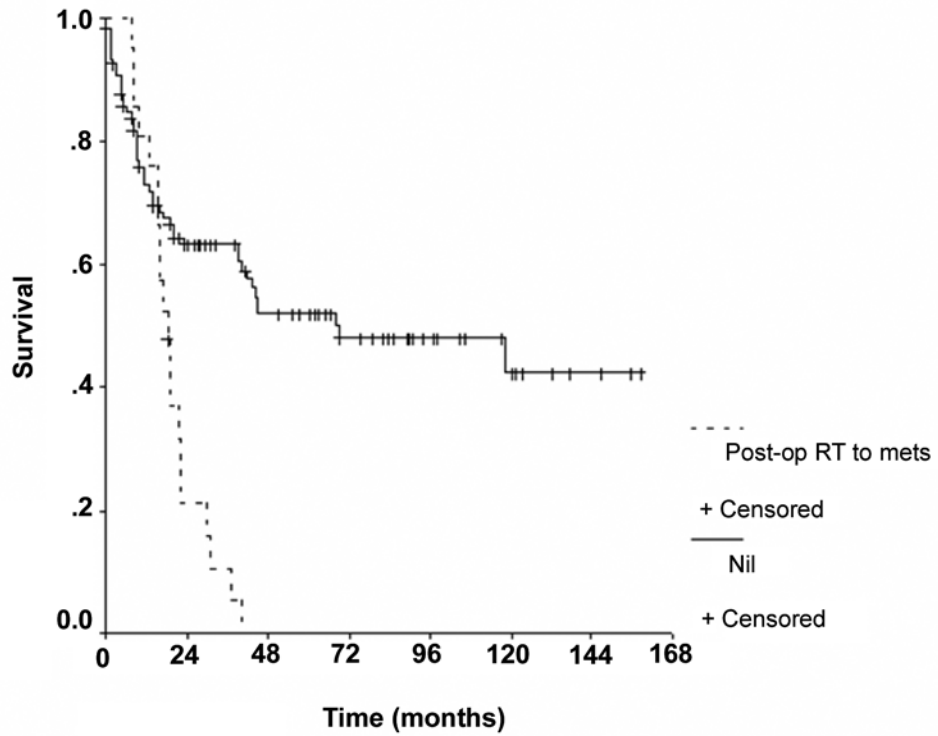


Figure 7 – Disease specific survival by postoperative radiotherapy to distant metastasis.

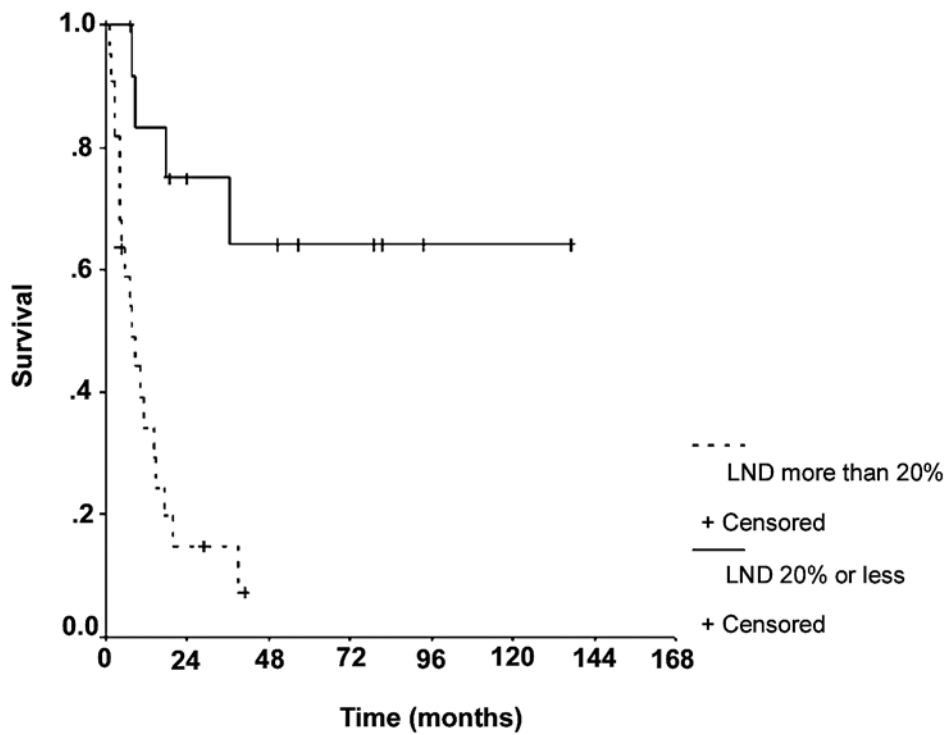


Figure 8 – Disease specific survival by lymph node density in node positive patients.

similar review in the literature. It is a heterogeneous group of patients as those receiving chemotherapy and RT were also included. The long recruiting period might involve variations in surgical techniques and treatment approach. Moreover, the number of lymph nodes resected in this review was also small. In order to achieve improvement in survival, Herr (4) observed that at least eight and nine lymph nodes should be removed, in node negative and positive patients, respectively. The corresponding figures in our series were respectively eight and seven. Despite these weaknesses, several prognostic factors, and in particular LND, were found to be predictive of disease specific survival.

An important finding was that N staging affected disease specific survival in univariate analysis but was replaced by LND in multivariate analysis. Moreover, neither the number of nodes involved nor the number resected affected survival in multivariate analysis. This implies that the concept of surgical margin can also be applied to the lymph node status, and residual disease in the lymph nodes should be avoided. This can be accomplished by a more extensive lymphadenectomy to include clinically undetected lymph node micrometastases and to reduce the LND. However, randomized trials comparing extended and standard lymphadenectomy are needed before concluding that extended lymphadenectomy improves disease specific survival.

The value and extent of pelvic lymphadenectomy during cystectomy were considered controversial in the eighties. Though complete pelvic lymphadenectomy was advocated by some authors (5), others concluded that its contribution to survival was minimal (6,7). There were also proponents of a more limited dissection of pelvic lymph nodes (8). The pendulum swung to the side for meticulous pelvic lymphadenectomy in the nineties (9-11). At the turn of the millennium, data on its morbidity (12) and lymphatic mapping (13-16) were evolving, together with other related concepts like sentinel nodes (15) and LND (4).

Stein (17) introduced the term LND though the concept had been previously mentioned by Herr (18) and Konety (19). He reported that for patients

with nodal disease, those with a LND of 20% or less had a 10-year recurrence free survival of 43%, compared to 17% of those with LND more than 20%. We also found in our study that a division line on LND at 20% discriminated patients with nodal disease into two groups with respect to disease specific survival, with both univariate and multivariate analyses. Sixty four point three percent of those with LND of 20% or less survived ten years or more, whereas all patients with LND more than 20% were either dead or censored at 39 months (Figure-8).

Our data showed that LND was a useful prognostic factor supplementary to N stage for disease specific survival. Future studies are needed before LND can be considered a widely accepted staging system or even used to replace the N staging. Moreover, the technique of lymphadenectomy, the way of counting the lymph nodes and the histological assessment should be standardized. Lymph node mapping studies (13-16) may facilitate extensive lymphadenectomy allowing, for example, one level higher resection.

Knowing that LND plays a crucial role in determining survival, it is important to define what pre-operative and intra-operative factors will predict LND. This will help to decrease the number of unnecessary cystectomy that will not offer advantage on disease specific survival. We analyzed by logistic regression the effects on LND by several pre-operative and intra-operative factors mentioned above. However, no such factor was found to predict LND in our series.

Our data showed that pT staging affected disease specific survival in univariate and multivariate analyses. This agreed with findings of other series in the literature and our survival figures were comparable to them (1). The marked difference in survival between pT2 and pT3 diseases as shown in Figure-2 may suggest that a more aggressive adjuvant approach should be adopted for extravesical disease.

Other factors that predicted disease specific survival in our series included post-operative RT to distant metastasis, surgical margin and CIS. Post-operative RT to distant metastasis also adversely affected survival in univariate and multivariate analyses. However, this might simply imply that

those that developed metastases and hence received palliative RT died earlier. A minimal or positive surgical margin was shown to affect survival only in univariate but not in multivariate analysis. This might be because the influence of surgical margin could be explained by other factors such as pT staging, for example. The paradoxical finding of higher disease specific survival associated to CIS just reached statistical significance with univariate analysis (log rank, $p = 0.0417$) and not with multivariate analysis.

We also specifically analyzed the effects of pre-operative and post-operative adjuvant therapy. Our results showed that chemotherapy did not alter the survival at all. Raghavan (20) pointed out that multi-center randomized trials had shown survival benefit from neoadjuvant chemotherapy while adjuvant chemotherapy failed to show such benefit. Similarly, our results showed that pre-operative RT to the bladder or post-operative RT to the pelvis did not alter the survival. In this regard, a meta-analysis by Shelley (21) showed a survival benefit with pre-operative RT plus radical cystectomy when compared to radical RT plus salvage cystectomy. As mentioned above, our finding that post-operative RT to distant metastasis predicted survival might simply imply that those who developed metastases died earlier.

CONCLUSIONS

In this retrospective review of radical cystectomy performed for TCC, pT stage, N stage, LND, CIS, surgical margin and post-operative RT to distant metastasis were found to predict disease specific survival. In particular, LND of 20% discriminated patients into two groups with respect to disease specific survival. The concept of LND may be useful in future staging systems and it shed a light on the importance of extended lymphadenectomy. This review of 133 patients failed to define any pre-operative and intra-operative factors that could predict LND. Future studies of larger scale may make this possible so as to decrease the number of unnecessary cystectomy that will not offer advantage on disease specific survival.

CONFLICT OF INTEREST

None declared.

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Correspondence address:

Dr. C. W. Cheng
 Department of Surgery
 The Chinese University of Hong Kong
 Prince of Wales Hospital, Hong Kong, China
 Fax: + 8 52 2635-9307
 E-mail: drcheng@hotmail.com

EDITORIAL COMMENT

In this study, the authors have reviewed an experience acquired over the last fourteen years in the management of bladder cancer by radical cystectomy. They looked at the usefulness of the lymph node density as the indicator of prognosis and the disease specific survival. Many factors can

influence the outcome of the patients with bladder cancer including T stage, N stage and the total number of lymph node retrieved.

A large number of publications have highlighted the importance of prognostic factor including age, gender and lymph node status and

evidenced that the number of the involved lymph nodes was the single most important prognostic variable.

Herr (1) introduced the term lymph node density indicating the ratio between the number of nodes removed to the number of nodes involved. They found that the ration based lymph node staging which reflect the quality of lymph node dissection was a significant variable prognostic for survival and local control of patients, which are left with node involvement after radical cystectomy.

Stein et al. (2) reported their experience of 244 patients with pathological lymph node metastases treated for primary carcinoma of the bladder. They reported that overall and recurrence free survival were significantly related to the pathological subgroup with the primary bladder tumor. Patients with lymph node

density of 20% or less had better recurrence free survival when compared to those with more than 20% (statistically significant). The total number of lymph nodes removed at surgery was also prognostic. Patients with 15 or less lymph nodes removed had 25% 10-year recurrence-free survival compared with 36% when greater than 15 lymph nodes were removed.

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Dr. Hammad M. Ather

Department of Surgery

Aga Khan University Hospital

Karachi, Pakistan

E-mail: hammad.ather@aku.edu

EDITORIAL COMMENT

The authors present their experience and clinical outcomes in 133 patients who underwent radical cystectomy for transitional cell carcinoma over a 13-year period of time. They found the pT stage and lymph node density and postoperative adjuvant radiotherapy to distant metastases were predictive of cancer specific survival. In addition, in those with lymph node positive disease a 20% lymph node density was an important risk stratifier.

The authors comment that radical cystectomy can reach good results with organ confined bladder cancer, which is true, however even those with locally advanced and with regional lymph node involvement benefit from a surgical approach with the best reported outcomes.

The median follow-up is very short and should be noted as potential weakness of the study.

Dr. John Peter Stein

Norris Comprehensive Cancer Center

University of Southern California

Los Angeles, California, USA

E-mail: stein@hsc.usc.edu

EDITORIAL COMMENT

The purpose of the manuscript was to determine the significance of lymph node density on survival of patients with transitional cell carcinoma of the bladder undergoing cystectomy. There are now 3 or 4 papers demonstrating the significance of lymph node density on recurrence and so this is a relevant paper and topic.

The study design in the most part supports the conclusion; however, the inclusion of patients receiving preoperative and postoperative chemotherapy (21 patients) and the 17 patients

receiving preoperative or postoperative radiotherapy to distant metastasis were included.

The main thrust of the paper was to determine the significance of lymph node density on survival. Only 11 patients had a lymph node density > 20%, with 108 presenting lymph node density < 20%. Reaching a conclusion on these 11 patients is concerning.

In conclusion, this is an interesting paper and certainly timely with all the data on the significance of lymph node density.

Dr. Stephen D. Beck

Department of Urology

Indiana University School of Medicine

Indianapolis, Indiana, USA

E-mail: stdbeck@iupui.edu

Salvage Radical Prostatectomy: An Alternative Treatment for Local Recurrence of Radioresistant Cancer

Marcos F. Dall'Oglio, Francualdo Barreto, Mario Paranhos, Adriano Nesrallah, Luciano Nesrallah, Miguel Srougi

Department of Urology, Faculty of Medicine, University of Sao Paulo (USP), Sao Paulo, Brazil

ABSTRACT

Objectives: The treatment of recurrent prostate cancer after radiotherapy or brachytherapy through radical prostatectomy has been little indicated due to the concern over the procedure's morbidity. We present the experience of our service with postradiotherapy radical prostatectomy.

Materials and Methods: Between 1996 and 2002, 9 patients submitted to radiotherapy due to prostate cancer were treated with salvage surgery for locally recurrent disease. All patients had a biopsy of the prostate confirming the tumor recurrence, increase in the PSA levels and staging without evidence of a systemic disease. We have assessed the morbidity and the recurrence-free survival rate after salvage radical prostatectomy.

Results: Preradiotherapy PSA varied from 6.2 to 50 ng/mL (mean 17.3) and clinical staging T1, T2 and T3 in 33.3%, 44.4% and 22.2% of the patients respectively. The interval for the biopsy after conforming external beam radiotherapy or brachytherapy varied from 8 to 108 months (median: 36). Four patients received antiandrogenic therapy neoadjuvant to the surgery with a mean of 7 months (1-48) after radiotherapy. From the six patients potent before the surgery, three have presented erectile dysfunction. Urinary incontinence as well as bladder neck sclerosis occurred in two patients (22.2%). Biochemical recurrence occurred in two individuals (22.2%) 12 months after the surgery. Biochemical recurrence-free survival rate was 77.8% with median follow-up time of 30 months (8-102).

Conclusion: Salvage radical prostatectomy is a safe and effective alternative for the treatment of locally recurrent prostate cancer after radiotherapy and brachytherapy.

Key words: *prostatic neoplasms; radiotherapy; recurrence; salvage therapy; prostatectomy*

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INTRODUCTION

The various forms of treatment for prostate cancer (PCa) include observation, external-beam radiotherapy, brachytherapy, cryotherapy, hormonal therapy and surgery, however, the decision of the ideal therapy should be individualized (1,2). Radical pros-

tatectomy (RP) presents a biochemical recurrence rate of 17 to 33% (3,4), while brachytherapy and external-beam radiotherapy 25 to 40% (5,6). The individuals that present an increase in their PSA level after radiation therapy and that are possible candidates to salvage radical prostatectomy (SRP) should be submitted to a new staging of the disease, since the in-

crease can indicate local recurrence, either systemic or both (2). Prostatic biopsy is positive in 80 to 100% of the cases (2,7), being fundamental the confirmation of the tumor for the therapeutic decision. Salvage procedures such as antiandrogenic therapy, radical prostatectomy and cryotherapy are options for patients with primary treatment failure. SRP has been efficient in the control of the disease in a period of time, with interesting results, reaching 82% disease-free survival rate in five years (8,9). However, SRP has not been getting more acceptance due to technical challenges of the procedure and significant morbidity, occurring urinary incontinence in 23 to 60%, rectal lesion in 15% and ureter lesion in 5% of the patients operated (8,10), with post-operative bladder neck sclerosis in up to 30% of the cases (10,11).

We have presented the results of SRP for radiotherapy recurring PCa treated in our institution.

MATERIALS AND METHODS

Nine men with mean age of 59 years (50-75), with biopsies confirming locally recurrent prostate cancer after conforming external beam radiotherapy (XRT) or brachytherapy (BT) were submitted to SRP between 1996 and 2002. Patients were considered candidates for salvage surgery when they presented a biopsy confirming the presence of a tu-

mor, increase in the PSA levels and absence of systemic disease, confirmed by bone scintigraphy, thorax radiography, tomography or magnetic resonance of the abdomen or pelvis with digital prostate examination at the physical exam. From the nine irradiated individuals, four received BT, four XRT and one was treated with both. Data regarding perioperative characteristics were assessed such as operative time, transoperative bleeding, blood transfusion and hospital stay. In the postoperative follow-up, the erectile function was analyzed by the penetration capacity with or without oral medication, urinary incontinence (> 1 pad/day) and bladder neck sclerosis in all individuals.

RESULTS

Mean follow-up was 30 months (8-102). Demographic data of the studied group are represented on Table-1 with preoperative and pathological Gleason score on Figure-1. Pathological stage was pT2N0 and pT3N0 in four and five patients respectively. Time interval after primary therapy (XRT or BT) for the beginning of antiandrogenic therapy was 1 to 48 months (median: 7 months) performed in four patients and the time to perform the prostate biopsy had a median of 36 months (8-108) after prostatic irradiation.

Table 1 – Demographic characteristics of treated patients with salvage radical prostatectomy.

Patients	Age (years)	Initial PSA (ng/mL)	Biopsy Gleason	Clinical Stage	Primary Treatment	ADT	Gleason in Specimen
AEB	59	6.2	8	T3b	BT	No	8
JFM	50	8.9	6	T1c	BT and XRT	Yes	6
OLM	63	50	5	T3a	XRT	Yes	8
JMN	65	24	5	T2a	XRT	Yes	7
RG	52	22	7	T2a	XRT	Yes	7
AGFR	62	10	7	T2a	BT	No	7
JDR	52	14	4	T1c	BT	No	8
JRLP	54	8.1	4	T2b	BT	No	7
SOL	75	12.6	6	T1c	XRT	No	9

ADT = antiandrogenic therapy neoadjuvant to surgery; BT = brachytherapy; XRT = external beam radiotherapy.

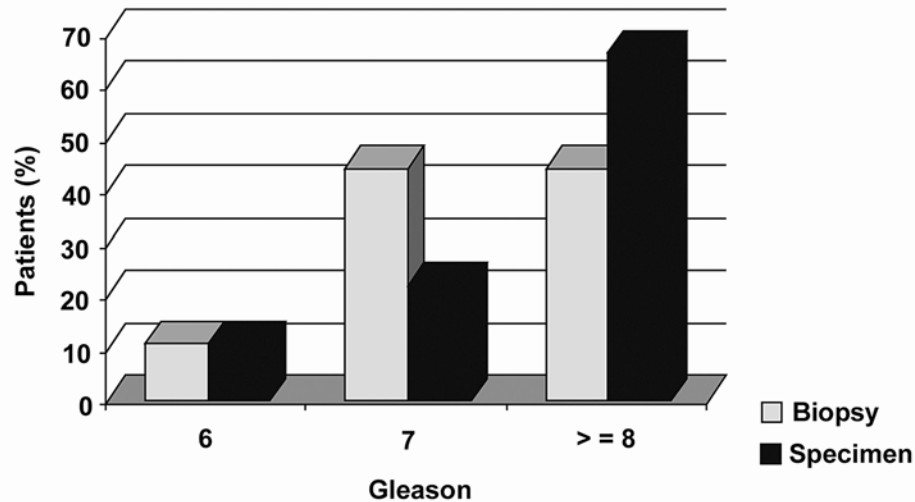


Figure 1 – Correlation between Gleason score at the biopsy and of the specimen.

SRP occurred normally, as Table-2 shows. Pathological staging revealed an organ-confined disease in four patients (44%), extra-prostatic extension occurred in five individuals (56%) and invasion of the seminal vesicles in three (33%). From the four patients that had organ-confined disease, three (75%) had biopsy Gleason score ≤ 7 . All three patients with compromised seminal vesicle presented biopsy Gleason score 7 or 8, while 60% of the patients with periprostatic extension presented a Gleason score 8. Organ-confined disease occurred in 75% of the patients with pre-radiotherapy PSA ≤ 10 ng/mL, with the compromise of the seminal vesicles occurred in all patients with PSA level above 20 ng/mL before radiotherapy.

From the nine analyzed patients, seven (78%) kept urinary continence, two presented bladder neck sclerosis (22%) two months after the surgery, and erectile dysfunction occurred in half of the patients (Table-3). Two individuals presented urinary incontinence after SRP, being one of them, after internal urethrotomy due to bladder neck sclerosis. Both were treated with artificial sphincter AMS 800. On Table-4, those results are compared to other series. After the SRP, biochemical recurrence occurred in two cases (22%) after a median time of 15 months requiring the introduction of antiandrogenic hormonal therapy.

Seven patients (78%) had the PSA less than 0.4 ng/mL, without any evidence of the disease, from which five (56%) without hormonal therapy. One patient with pre-XRT PSA levels of 50 ng/mL, clinical stage T3c, presented a recurrence in retroperitoneal lymph nodes, being submitted to cytotoxic chemotherapy followed by radiotherapy in the areas of compromised lymph nodes. All patients are alive after a median follow-up time of 30 months (8 to 102 months).

Table 2 – Transoperatory parameters and hospital stay.

Parameters	Mean (variation)
Operative time (minutes)	168 (120 - 240)
Bleeding estimation (mL)	433 (380 - 510)
Blood transfusion	-
Hospital stay (days)	4.8 (4-7)

Table 3 – Postoperative complications.

	N (%)
Sexual impotence	4 (50)
Bladder neck sclerosis	2 (22)
Urinary incontinence	2 (22)

DISCUSSION

In this series from the nine patients treated with radical prostatectomy for locally recurrent cancer after primary radiotherapy 78% had disease control, 22% urinary incontinence and 50% erectile dysfunction. Five patients (56%) had no adjuvant treatment without evidence of the disease. SRP was performed without transoperative complications, without the need for blood transfusion and presenting a cancer specific survival rate of 100% in the median follow-up time of 8 years (8-102 months).

SRP, even though associated to a larger control of the prostate cancer locally recurrent after radiotherapy, has received limited attention in the urologic field due to technical challenges during surgery and the potential risk of complications such as urinary incontinence, impotency, bladder neck sclerosis and both rectal and ureteral lesions (8,9). Urinary incontinence after SRP has been much more frequent than in conventional radical prostatectomy that varies between 5 and 31% (12), representing a limiting factor for salvage surgery, since the urinary incontinence in this study was 22%, similar to other series with a variation of 16 to 45% (9,10,12). The insertion of the artificial sphincter AMS 800 in the cases of persisting urinary incontinence has offered good results in most of the cases (13), this resource was used in two cases resolving urinary leaks.

This study demonstrates an acceptable complication rate making the results similar to a conventional radical prostatectomy. Mean operative time was of 168 minutes and bleeding mean of 433 mL, with

mean hospital stay of 4.8 days, similar to other series (9,10). Vaidya & Soloway reported a mean hospital stay of three days (9). Rectal lesion did not occur in our initial SRP experience, being in agreement with the reports of up to 0.6% during conventional radical prostatectomy (14). By analyzing the SRP series the rectal lesion may occur between 2 to 15% and ureteral lesion 5% of the cases, respectively (8,10).

The risk of bladder neck sclerosis is substantially high after the SRP (2), the rate of 22% of the study is similar to those observed by other authors as Table-4 (8,10,11,15) shows. According to the results obtained in other studies, bladder neck sclerosis after conventional radical prostatectomy carries between 1 to 4% (16,17), however, Touma et al. reported an incidence of 17.5% after SRP (12). Bladder neck sclerosis after radiotherapy can be a problem of difficult solution, sometimes requiring more complex procedures for an adequate correction such as appendicovesicostomy or ileovesicostomy as described by Pisters et al. (18).

Erectile dysfunction is considered an inevitable consequence of the SRP, even though preservation of cavernous nerves is possible. When it is possible to preserve neurovascular bundles bilaterally, up to 70% of the patients recuperate their sexual function (10,17) and urinary continence (10). In this work the erectile function was preserved in half of the patients previously potent before the surgery.

Clinical stage of post-radiotherapy recurrent prostate cancer is a predictive factor for disease free survival rate (2,12,15), even though Rogers et al. (8) have not observed this correlation (8). In our series,

Table 4 – Associated morbidity with salvage radical prostatectomy.

References	N	Urinary Incontinence (%)	Bladder Neck Sclerosis (%)	Rectal Lesion (%)	Biochemical Recurrence (%)
Rogers et al. (8)	40	58	27	15	18
Amling et al. (11)	108	51	21	6	43
Stephenson et al. (10)	100	23	30	2	34
Vaidya (9)	6	16	0	0	16
Gheiler et al. (14)	40	50	16	3	53
Present study	9	22	22	0	22

44% of the cases of the disease were organ-confined and the involvement of seminal vesicles occurred in 33% of the individuals. In similar studies those findings occurred in 39% and 30% of the cases, respectively (15). Preoperative PSA levels inferior to 10 ng/mL have a strong correlation to organ-confined disease and higher progression-free survival rate. (2,8,11,12).

Cryotherapy is a viable alternative in the treatment of radioresistant prostate cancer, however, urinary incontinence and bladder neck sclerosis rates are 73% and 44% respectively. Besides, pelvic pain, dysuria, hematuria, bladder neck sclerosis and urethral fistula are other potential complications of cryotherapy (19). Another discouraging factor is the reduced control of cancer in relation to SRP (2,12,19).

In this study 55.5% of the individuals were recurrence-free. SRP is a viable and safe alternative to the treatment of radioresistant cancer, however the selection of cases with PSA < 15 ng/mL and Gleason score ≤ 7 offer better results without the need of associated androgenic blockage.

CONFLICT OF INTEREST

None declared.

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Correspondence address:

Dr. Marcos F. Dall'Oglio
Rua Barata Ribeiro, 398 / 5o. Andar
São Paulo, SP, 01308-000, Brazil
Fax: + 55 11 3159-0994
E-mail: marcosdallogliouro@terra.com.br

EDITORIAL COMMENT

The authors report on excellent results with post-radiotherapy salvage radical prostatectomy in nine patients. Some considerations can be done, regarding the results obtained herein.

First, one remarkable aspect of the study is the young age range of the patients submitted to salvage radical prostatectomies in this series. Of the nine men, five were under 60 years of age at the time of salvage surgery. Considering that the median time from initial treatment to the establishment of therapeutic failure was 36 months, we can conclude that most patients were really young when receiving the initial radiation treatment. May be that the best window for cure was lost then for these men.

A second intriguing finding is the very low complication rate associated to salvage surgery in the published series, which is considerably lower than that of historical series of greater patient volumes. Urinary incontinence, which approaches 60% in historic series, was observed in only 22% in this study.

Rectal injuries, also reported in larger series (around 10% at Wayne State), (1) were absent here. Besides, the authors reported excellent potency rates, something unexpected in this kind of surgery. This may indicate one of two things: either a low generation of fibrosis by the radiation treatments received or an exceptional surgical technique. This is also confirmed by the lack of transfusions and by the reduced operative time (mean 168 minutes).

Recent data suggest that salvage radical prostatectomy may be a very good option to patients with biochemical failure after initial radiation treatment. This year, the group from Mayo Clinic reported on the results of 138 patients submitted salvage radical prostatectomy, with 65% cancer-specific survival rates (2). Approximately 70% of patients remained continent or in need of one pad/day; transfusion rates were 36%, rectal injuries occurred in 4%, and bladder neck sclerosis in 22%. The conclusions of the authors were that results improved with time, and that

salvage surgery should be offered to Young men with at least 10-year life expectancy and organ-confined disease.

In a setting in which the media easily distorts scientific truth, we have observed growing numbers of non-surgical options for the initial treatment of younger men with clinically localized prostate cancer. In this situation, the favorable results of salvage surgery are welcome. However, we do not know yet whether the results of this Brazilian study (with small numbers, in fact) or the results of the Mayo Clinic are really reproducible by all our urologic surgeons. Probably, our best strategy concerning this subject

would be to inform our urologists that, as we see in muscle-invasive bladder cancer, surgery is still the best initial chance of cure for young men with biologically aggressive prostate cancer.

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Dr. Gustavo Franco Carvalhal
Section of Urology, Catholic University
Porto Alegre, RS, Brazil
E-mail: gcarvalhal@terra.com.br

Eggshell Calcification of Kidney in Ureteropelvic Junction Obstruction

Narmada P. Gupta, Rajiv Yadav

Department of Urology, All India Institute of Medical Sciences, New Delhi, India

ABSTRACT

Eggshell calcification of kidney in case of ureteropelvic junction obstruction (UPJO) is an uncommon finding with only a few cases reported in literature. We report a thirty-year-old symptomatic man with curvilinear calcification in hydronephrotic right kidney. Thorough investigations to rule out genitourinary tuberculosis and hydatid disease of kidney were performed prior to the definitive management by laparoscopic approach.

Key words: ureter; hydronephrosis; kidney pelvis; calcinosis
Int Braz J Urol. 2006; 32: 557-9

INTRODUCTION

Eggshell calcification of kidney in case of ureteropelvic junction obstruction (UPJO) is an uncommon finding. Such kind of curvilinear calcification is more commonly found in benign cysts, renal cell carcinoma and hydatid cyst. We report a thirty-year-old symptomatic man with eggshell calcification in hydronephrotic right kidney. Progressive deposition of calcium salts in a chronically dilated renal parenchyma may have caused calcification in the hyalinized fibrous renal tissue.

CASE REPORT

A thirty-year-old man was investigated for abdominal pain and a palpable mass in the right lumbar region. He had no associated urinary symptoms or bowel dysfunction. The only significant

history was a pulmonary tuberculosis ten years before for which he was adequately treated. He had no history of any operative intervention or trauma in the past. On physical examination, he was normotensive and had a 7cm hard, nontender bimanually palpable lump with restricted mobility in the right lumbar and umbilical region. No bruit was present over the lump. An investigation revealed a normal urine routine and microscopic examination, sterile urine culture and a normal hemogram. Serum creatinine, blood urea nitrogen and serum calcium were unremarkable. Urine for acid-fast bacillus microscopy was negative thrice and urine polymerase chain reaction for *Mycobacterium tuberculosis* was also negative. Indirect hemagglutination test for hydatid was negative. KUB film revealed an eggshell like calcification in the right kidney region (Figure-1). Subsequent ultrasound and computerized tomography showed a well defined, cystic right kidney (Figure-2). Renal scan confirmed the absence of any functional renal parenchyma on the right side. On

cystoscopy, the right orifice was normal and no urine flow was detected. Right retrograde pyelogram revealed a thin ureter, which was obstructed at the ureteropelvic junction. Laparoscopic nephrectomy was done. Multiple sections examined showed a fibrocollagenous cystic wall with hyalinization, calcification and ossification. Certain areas with intact epithelial lining and thyroidization of renal tubules were also observed. No granulomatous inflammation or parasite was present.

COMMENTS

Calcification of kidney associated to ureteropelvic junction obstruction (UPJO) is rare and only a few cases have been reported in literature (1). Although such eggshell calcification is usually observed in benign condition, surgical intervention may still be indicated as the risk of malignancy in such lesion is 20% (2). Interestingly, Gold et al have



Figure 1 – Kidneys, ureters and bladder X-ray showing eggshell calcification in the region of right kidney.

described a case of UPJO with a calcified renal pelvis and superimposed spindle urothelial carcinoma (3).

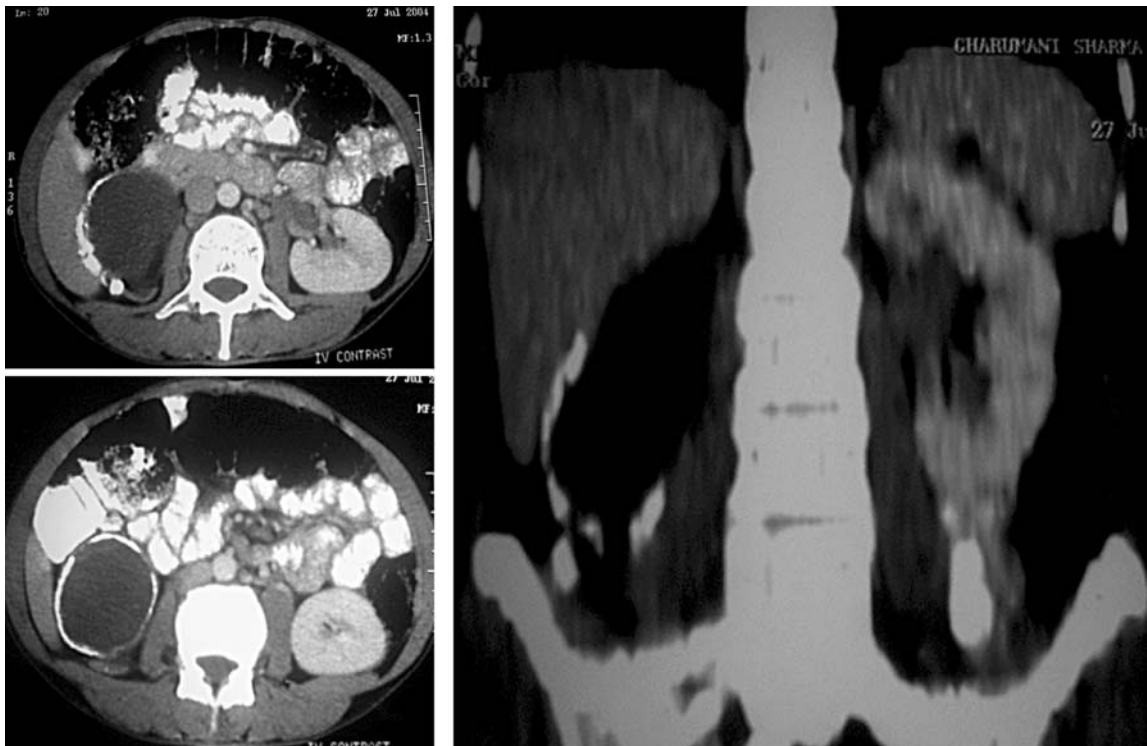


Figure 2 – Computerized tomography showing calcified right hydronephrotic kidney.

Calcification in this situation occurred despite normal serum levels of calcium probably due to progressive deposition of calcium salts in damaged and hyalinized tissue in the wall of chronic hydronephrotic kidney.

CONFLICT OF INTEREST

None declared.

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Correspondence address:

Dr. Narmada P Gupta
Head, Department of Urology
All India Institute of Medical Sciences
Ansari Nagar, New Delhi 110029, INDIA
Fax: + 91 11 686-2663
E-mail: narmadagupta@hotmail.com

Complete En Bloc Urinary Exenteration for Synchronous Multicentric Transitional Cell Carcinoma with Sarcomatoid Features in a Hemodialysis Patient

Tiberio M. Siqueira Jr, Evandro Falcao, Tiberio M. Siqueira

Memorial Sao Jose Hospital, Recife, Pernambuco, Brazil

ABSTRACT

The incidence of transitional cell carcinoma (TCC) in patients submitted to hemodialysis is low. The presence of TCC with sarcomatoid features in this cohort is even scarcer. Herein, we describe a very rare case of synchronous multicentric muscle invasive bladder carcinoma with prostate invasion in a hemodialysis patient, submitted to complete en bloc urinary exenteration.

Key words: *hemodialysis; urologic neoplasms; carcinosarcoma; bladder; surgery*
Int Braz J Urol. 2006; 32: 560-2

CASE REPORT

A 58 years-old white obese man, submitted to a hemodialysis program due to diabetic nephropathy, was referred to our department because of painless macroscopic hematuria.

Ultrasound and cystoscopy revealed multiple pediculated and sessile lesions in different parts of the bladder. Pre-operative computed tomography (CT) scan showed no extravesical dissemination or node enlargement.

The patient was submitted to a deep transurethral resection of bladder tumor (TURb) in part of the visible masses, but not all due to its extent. Pathologic examination showed high-grade urothelial tumor, with invasion of the lamina propria layer only.

Based on the pathological report, the patient was submitted to en bloc urinary exenteration associated to extended pelvic lymphadenectomy (Figure-1). Operative time, blood loss and hospital stay were

300 minutes, 770 mL and 5 days, respectively. No complications were observed.

Final pathology evidenced high-grade muscle invasive bladder carcinoma with extravesical invasion to adipose tissue and bladder neck. Prostate invasion by the urothelial tumor was observed, presenting sarcomatoid features (Figure-2). Surgical margins, kidneys, ureters and nodes were free of tumor. No chemotherapy treatment was administered.

On postoperative month 6, CT scan showed multiple lesions in both lungs and brain. Pleural biopsy evidenced bladder tumor metastasis. Six days later, the patient died of metastasis complications.

COMMENTS

It is well known that uremic patients have a higher risk to develop cancer, in which the most common types are the urological ones (1).

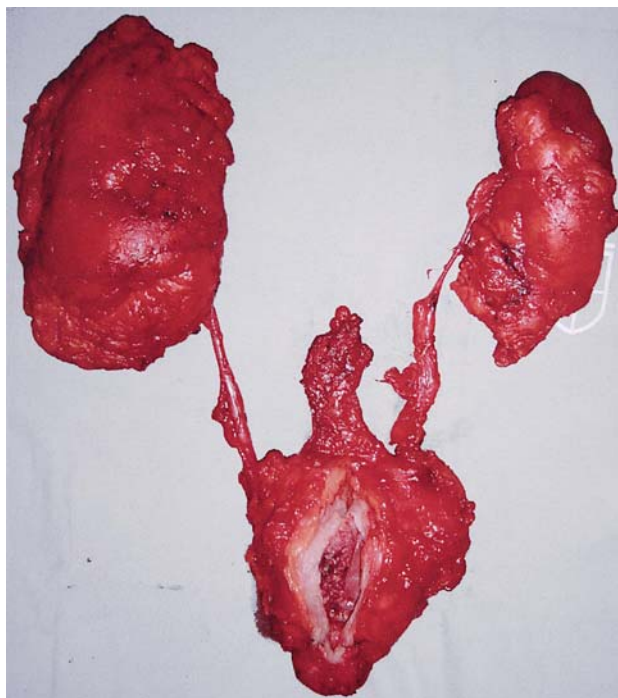


Figure 1 – Surgical specimen shows the complete en bloc removal of the entire urinary tract and prostate, associated to extended pelvic lymphadenectomy.

Recently, Wu et al. (2) reported the largest experience ever published with hemodialysis patients presenting TCC. In all 30 cases, the initial diagnosis

presented gross hematuria as a cause. According to final surgical status, the patients were divided in 6 different groups. Groups 1 and 2 had total urinary exenteration (11 cases). Groups 3 and 4 had uni or bilateral nephroureterectomy with bladder cuff excision (13 cases). Group 5 had only TURb and group 6 with one case of radical cystectomy and ileal conduit.

The authors observed 100% incidence of recurrence rate in the patients of group 2, leading to a stepwise total exenteration. Likewise, the recurrence rate in groups 3,4 and 5 were 2.3, 1.7 and 1.8 times, respectively. Finally, the treatment administered to patients in group 6 was considered not ideal, due to the inability in monitoring recurrences. The conclusion was that no matter what the tumor grade, stage or location, the treatment of choice for hemodialysis patients presenting TCC is total urinary exenteration.

In our case, every definitive forms of treatment were discussed with the patient. Besides that, the low residual urinary output led us choose the total “en bloc” urinary exenteration. For our surprise, final pathology showed a MIBC with sarcomatoid features and prostate invasion.

No chemotherapy was prescribed, based on the final pathological report and the patient’s clinical status. The rapid progression to lungs and brain metastasis, show the aggressiveness of the tumor and made us wonder if chemotherapy would avoid this final course.

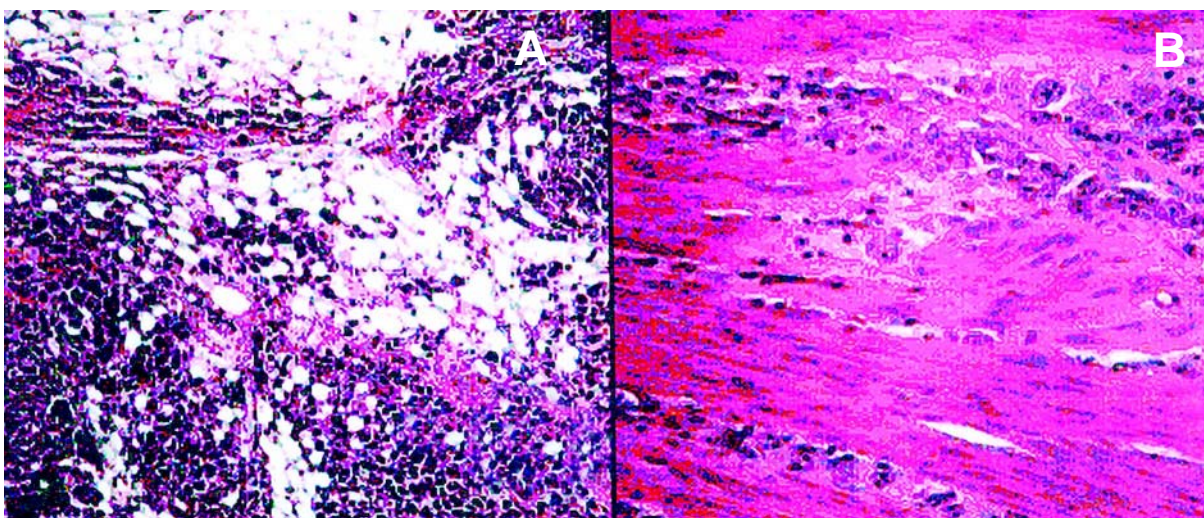


Figure 2 – Pathologic analysis. A) High grade muscle invasive bladder carcinoma with extravesimal invasion to adipose tissue and bladder neck. B) Prostate invasion by urothelial tumor presenting sarcomatoid features (HE, X133).

This case corroborates with the need to evaluate every patient in hemodialysis presenting hematuria in order to diagnose TCC. To the best of our knowledge, this is the first report of synchronous multicentric MIBC with sarcomatoid features and prostatic invasion that is treated by total “en bloc” urinary exenteration. Depending on clinical status, chemotherapy should be considered.

ACKNOWLEDGEMENT

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CONFLICT OF INTEREST

None declared.

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Correspondence address:

Dr. Tibério M Siqueira Jr
Av. Agamenon Magalhães, 4775 / 201
Recife, PE, 50070-160, Brazil
E-mail: tiberiojr@uol.com.br

Sarcomatoid Carcinoma with Osseous Differentiation in the Bladder

Luis F. Arenas, Dercilio A. Fontes, Emilio M. Pereira, Flavio L. Hering

Portuguese Beneficent Hospital, Sao Paulo, SP, Brazil

ABSTRACT

Introduction: Bladder sarcomatoid carcinoma is a very rare variant of transitional cell carcinoma. With disputed nomenclature, the tumor has been described previously under a variety of names such as sarcomatoid carcinoma, pseudosarcoma, malignant mixed mesodermal/Müllerian tumor, metaplastic carcinoma and spindle cell carcinoma. This malignancy represents 0.3% of all bladder tumors and has an aggressive behavior yielding a poor prognosis despite radio and chemotherapy.

Case Report: An 81 y/o man presented with a transitional cell carcinoma and underwent a transurethral resection. Adjuvant onco-BCG was introduced. After 9 months of follow-up, a local tumoral recurrence occurred and a new transurethral resection revealed sarcomatoid carcinoma with osseous elements. A radical cystoprostatectomy was then carried out.

Key words: *bladder neoplasms; transitional cell; BCG vaccine; carcinosarcoma; cystectomy*
Int Braz J Urol. 2006; 32: 563-5

INTRODUCTION

Sarcomatoid carcinoma (SC) of the urinary bladder is a variant of Transitional Cell Carcinoma (TCC). SC contains sarcoma-like areas with either spindle or pleomorphic cells. The aggressive behavior of the tumor precludes radical therapy whenever possible, since adjuvant therapy seems to have little effect on the tumor natural history. We report on a case of SC with osseous element, with emphasis on the peculiar clinical and histopathological features.

CASE REPORT

A 81-year-old man presented with irritative lower urinary tract symptoms. Ultrasound showed thickening of the right posterior bladder wall and a

cystoscopy revealed a 3 cm hyperemic verrucous lesion. Transurethral resection of the lesion was performed and the histopathology revealed a TCC with no muscle invasion. The patient presented hematuria 9 months later and a cystoscopy revealed a 5 cm tumor in the right bladder wall. Onco BCG (Bacilli Calmette-Guérin), 40 mg once a week for 8 weeks was successfully administered. Seven months later, the patient presented hematuria again. A cystoscopy with biopsy revealed a high grade, muscular invasive TCC with a pattern of sarcomatoid carcinoma with osseous differentiation. Radiotherapy had no effect. Radical cystoprostatectomy was performed with an uneventful follow-up. The surgical specimen revealed a tumoral mass of 9 cm in diameter with a histopathologic pattern of a high grade TCC (Figure-1) with osteosarcomatous heterologous elements (Figure-2). Adjacent fat tissue was tumor free. A month later, a

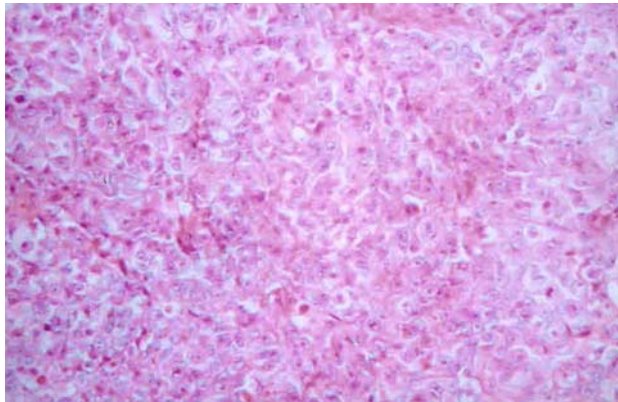


Figure 1 – Area of high grade urothelial carcinoma of the urinary bladder (HE, X100).

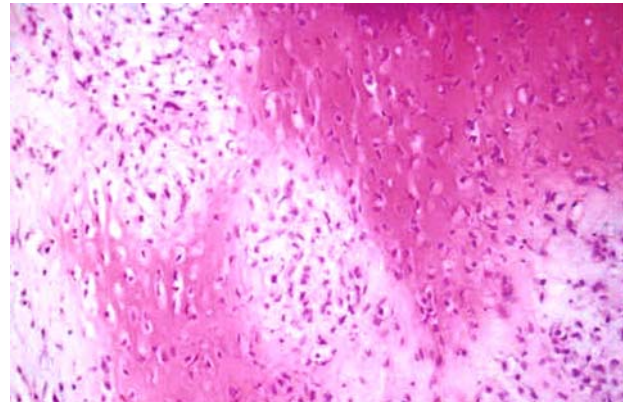


Figure 2 – Bone differentiation beside areas of poorly differentiated carcinoma (HE, X100).

chest X-ray showed multiple pulmonary nodules consistent with metastases and died 2 months after this diagnosis.

DISCUSSION

Bladder SC is an uncommon tumor. Fewer than 70 cases of primary heterologous carcinosarcoma of the urinary bladder have been reported. Terminology for this tumor has been varied and some authors define SC as a tumor that contains further mesenchymal elements in addition to spindle cells.

The presence of spindle cell in a urinary bladder TCC warrants the designation of SC and some authors define carcinosarcoma as an admixture of malignant epithelial and malignant soft tissue elements (1). Grossly these tumors tend to be polypoid and ulcerated. At histology, the cellular arrangement may have various patterns such as that of the fascicular or storiform appearance of a leiomyosarcoma or malignant fibrous histiocytoma. For a carcinosarcoma, the stem cell from which the epithelial and mesenchymal components are derived is expected to be more immature than the epithelial stem cell from which different components of sarcomatoid carcinoma originate, since in the latter, immunohistochemical or ultrastructural epithelial characteristics are still detectable. However, comparative genomic hybridization strongly suggests a monoclonal origin for all those tumors (2).

The tumor has poor prognosis. Records of Mayo Clinic (1936-1995) preclude that the tumors occur predominantly in male smokers, mean age of 72 years (1). Signs and symptoms include clath hematuria, dysuria, pollakiuria and urinary infection. At initial diagnosis, almost all patients have advanced stage disease with muscularis mucosa involvement. Most patients died of local disease or of lymph node, lung, pleura, brain, liver and bone metastases.

Radical cystoprostatectomy should always be considered to bladder SC. Froehner et al. (3) reported a case of a metastatic SC remission of the bladder with cisplatin and gemcitabine, although, in the literature, adjuvant radiotherapy or adjuvant chemotherapy are apparently of no effect.

CONFLICT OF INTEREST

None declared.

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Correspondence address:

Dr. Luis Fernando Arenas
Urologisches Klinikum
Heinrich-Heine Universität Düsseldorf
Steinbrinkstrasse, 96a
46145, Oberhausen, Germany
E-mail: luis64@ig.com.br

Small Round Blue Cell Tumor of Seminal Vesicle in a Young Patient

Adriano A. de Paula, Adriano R. Maltez, Eliane D. Mota

Sections of Oncological Urology and Pathology, Araujo Jorge Hospital, Goiania, Goias, Brazil

ABSTRACT

Seminal vesicle tumor is a rare disease with unclear origin. Generally, it is presented as a pelvic mass that can be detected by sonography and digital rectal exam. The authors report a 25-year-old patient with a pelvic mass which the magnetic resonance and surgical specimen reveal a seminal vesicle tumor. Immunohistochemical findings favored a primitive neuroectodermal tumor of the seminal vesicle. Herein, the treatment, histological and histochemical findings of this entity are discussed.

Key words: seminal vesicles; neuroectodermal tumors; urogenital neoplasms
Int Braz J Urol. 2006; 32: 566-9

INTRODUCTION

Seminal vesicle tumors are rare malignancies, usually carcinomas and are generally presented as a retrovesical mass that can be detected by digital rectal examination and sonography (1). Small round blue cell tumors (SRBCT) is a group of neoplasms that share a common and unique chromosomal translocation and include the primitive neuroectodermal tumor (PNET) and the Ewing's sarcoma family. PNET typically develops in pediatric population, arising from the thoracic region, but genitourinary involvement in adulthood is uncommon.

CASE REPORT

A 25-year-old man underwent abdominal sonography due to epigastric pain which showed a complex-cystic mass with 5,0x 4,9x 5,5cm in the topography of seminal vesicles. A pelvic computerized

tomography confirmed a solid retrovesical lesion. The patient declined an ultrasound guided trans-rectal biopsy and never returned during a 12 month-period. After this period he returned complaining of rectal stricture, and lower urinary obstructive symptoms.

Pelvic magnetic resonance showed a 17 cm retrovesical mass (Figure-1) and a trans-rectal ultrasound guided biopsy revealed small round cells for which immunohistochemical findings suggested a primitive neuroectodermal tumor diagnosis. Two cycles of neo-adjuvant chemotherapy consisting of vincristine, cyclophosphamide, doxorubicin, ifosfamide and etoposide were performed, resulting in no radiological response.

Workup for metastasis was negative and the patient underwent laparotomy with resection of the mass. The tumor did not infiltrate adjacent organs and the surrounding desmoplastic reaction allowed negative surgical margins with prostate, bladder and rectum preservation.

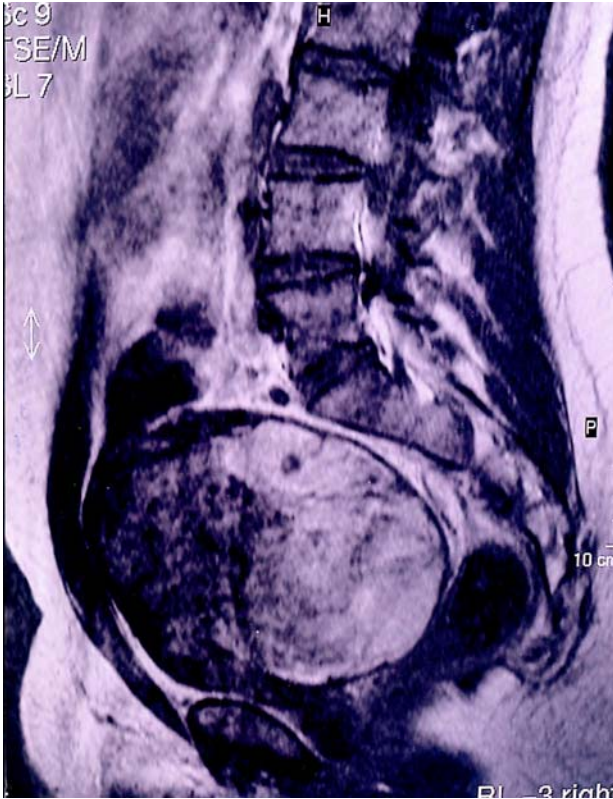


Figure 1 – Magnetic resonance imaging of the pelvis showing seminal vesicle tumor.

Histological exam showed an enormous amount of necrosis and hemorrhage intermixed by a monotonous pattern of small round blue cells with discreet pleomorfism, clear cytoplasm, solid block setting with cystic areas and fibrous collagenized stroma (Figure-2). Immunohistochemical examination was positive for CD-99 (Figure-3) and S-100 protein while muscular actin, gp100 antigen, CD34, Desmin, Melan A/MART-1, EWS-FLI1, Alpha-Inibin and Calreatin were negative. Focally positive staining for cytokeratin 40, 48, 50 and 50.6 KDa was found. The combination of the histological and immunohistochemical results led to the diagnosis of a PNET. Reciprocal translocation $t(11;22)(q24;q12)$ using transcriptase-reverse Polymerase Chain Reaction (RT-PCR) was inconclusive in the present study due to the lack of PGK1 and ACBT genes amplification of the surgical specimen.

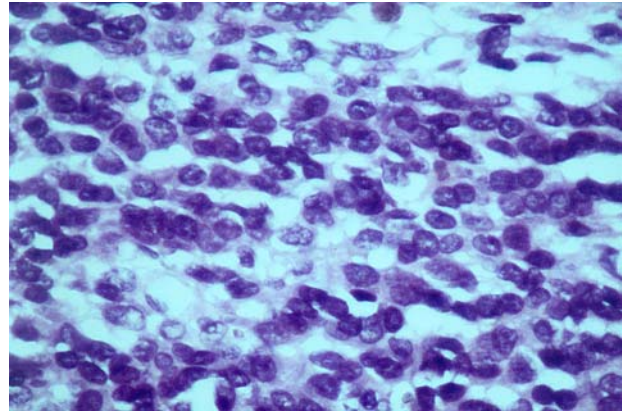


Figure 2 – Histological analysis showing a monotonous pattern of small round cells (HE, X400).

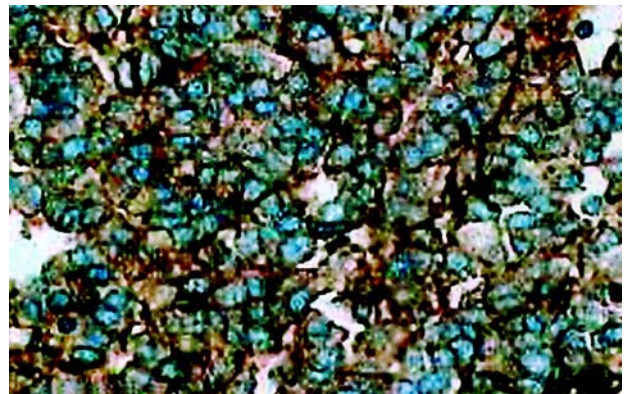


Figure 3 – CD99 positivity (Immunohistochemical staining, X100).

After a three years follow up, the patient remained potent, with normal urinary and digestive functions and showed no relapse.

COMMENTS

Genitourinary origin of PNET is rare and diagnosis is difficult and usually confused with primary rectum or prostate carcinomas, benign tumors (1) or with other small round blue cell tumors (SRBCT). Differential diagnosis must include Ewing's sarcomas, peripheral medulloepithelioma, rhabdomyosarcomas, myxoid liposarcomas, malignant fibrous his-

tiocytomas chondrosarcomas, lymphoblastic lymphoma and even small cell osteosarcomas and neuroblastomas. Differential diagnosis must also include benign conditions like prostatic utricle cyst, prostatic abscess, seminal vesicle hydrops, seminal vesicle cyst, seminal vesicle empyema, ectopic ureterocele, fibrous obturator fossa cyst, hemangiopericytoma, among others (2).

Some genitourinary PNETs have already been reported arising from kidney, adrenal gland, prostate, spermatic cord and testis, but to the best of our knowledge, up to now, no seminal vesicle origin has been published.

Although PNETs can be accurately diagnosed using time-honored morphologic criteria and immunohistochemistry, the genetic confirmation of the translocation t(11;22)(q24;q12) by cytogenetics and/or molecular analysis is essential for the diagnosis of unusual morphologic variants, including adamantinoma-like, spindled, esclerosis and clear cell/ anaplastic variants (3). CD99 expresses protein product of the fusion gene EWS/FLI-1 and are often positive in PNET, SRBCT and Ewing's sarcoma family. The combination of histological, immunohistochemical and, sometimes, cytogenetics leads the final diagnosis. In the present case, despite the lack of cytogenetic confirmation of the reciprocal translocation t(11;22)(q24;q12), the positivity of CD99 and S-100 protein in the immunohistochemical exam and the histological presentation favored PNET diagnosis.

The biological behavior of this tumor is expressed by a rapid growing mass non-responsive to

chemotherapy and frequently associated to distant metastasis. The presence of an extensive area of necrosis in histopathological exam means that there might have been an expressive response to the neoadjuvant chemotherapy, which was clinically reflected by a favorable evolution regarding relapse and survival.

Surgical approach is the best treatment modality and new chemotherapy agents are necessary to achieve better results in metastatic disease.

CONFLICT OF INTEREST

None declared.

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March 5, 2006*

Correspondence address:

Dr. Adriano A. Peclat de Paula
Seção de Onco-Urologia, Hospital Araújo Jorge
Rua 239 / 181 - Setor Universitário
74605-070, Goiânia, GO, Brazil
E-mail: adrianopaula@brturbo.com.br

EDITORIAL COMMENT

Primary seminal vesical tumors either benign or malignant are very rare. Primary adenocarcinoma of the seminal vesicle is a rare tumor. Only 50 cases have been reported in literature. Differential diagnosis includes carcinoma extending from the urinary bladder, prostate, or rectum. Cystadenomas may be incidentally discovered on rectal examination or at autopsy in middle-aged men, or the patients may present hemospermia or nonspecific suprapubic pain. Epithelial-stromal tumors of the seminal vesicle include a spectrum of tumors that grossly and microscopically resemble the similarly named tumor of the prostate, and fibroadenoma and phyllodes tumor of the breast. The distinction between cystadenoma and epithelial-stromal tumor of the seminal vesicle is based on the microscopic aspect of the stroma: normal or possibly reactive smooth muscle favors cystadenoma and hypercellular, presumably neoplastic stroma favors epithelial-stromal tumor.

Other tumors are equally very rare. The present report is a unique case of primary small

round undifferentiated tumor of the seminal vesicle. There is a spectrum of tumors showing small round undifferentiated cells including T lymphoblastic lymphomas, poorly differentiated synovial sarcomas, some neuroendocrine carcinomas, rare cases of rhabdomyosarcoma usually of alveolar type and the primitive neuroectodermal tumors (PNET). The latter having been the source of both controversy and rapid advances in recent years but the term PNET is now the preferred term to describe a family of lesions that are characterized by a specific and reproducible reciprocal chromosome translocation, t(11;22)(q24;q12). These tumors show morphologic, immunohistochemical, ultrastructural and tissue cultural evidence of neuroendocrine differentiation. In the present case, in spite of lack of cytogenetic confirmation of the reciprocal translocation, the positivity of CD99 and S-100 protein in the immunohistochemical exam and the histological features favor the diagnosis of PNET.

Dr. Athanase Billis

Full-Professor of Pathology

State University of Campinas, Unicamp

Campinas, São Paulo, Brazil

E-mail: athanase@fcm.unicamp.br

Early Successful Orchidopexy Does Not Prevent From Developing Azoospermia

Faruk Hadziselimovic

Kindertagesklinik Liestal, Liestal, Switzerland

ABSTRACT

Introduction: The incidence of Ad spermatogonia (stem cells for fertility) was assessed in 20 cryptorchid patients, all of whom had a successful orchidopexy in childhood but developed azoospermia following puberty.

Materials and Methods: From a cohort of 231 patients who had a semen analysis following successful orchidopexy 20 patients (9%) had azoospermia. The patients were classified into 2 groups according to the time of surgery: A = < 21 months of age (n = 5, mean = 10.7 ± 8.6 months) and B = during childhood (n = 15, mean = 10.1 ± 3 years). Nine of the 20 patients (45%) had bilateral cryptorchidism: A = 1 and B = 8. Testicular biopsies were performed during orchidopexy and analyzed with semi-thin technique. The number of Ad spermatogonia and entire number of germ cells was determined. The patients' semen analyses were evaluated at least twice; FSH and testosterone plasma values were estimated.

Results: In group A, all patients had germ cells at the time of surgery (mean = 1.04 ± 1.4 germ cells per tubular cross section); only 6 patients in group B (40%) had no germ cells (mean = 0.17 ± 0.4); A vs. B, $p = 0.0133$. Importantly, Ad spermatogonia were absent in the entire study population. The plasma FSH of 16 patients (80%) was abnormal [median = 16.35 IU/L (Interquartile range of sample - IQR 9.075-27.85 95% CI, 3-53)] while the plasma testosterone of all the patients was normal.

Conclusions: The most severe cause of infertility in cryptorchid patients cannot be mitigated by an early successful surgery alone.

Key words: testis; cryptorchidism; surgery; germ cells; infertility; azoospermia

Int Braz J Urol. 2006; 32: 570-3

INTRODUCTION

Cryptorchidism is accountable for 8% of all sterile patients and for 20% of those with azoospermia (1). Cryptorchidism, therefore, is one of the most common etiology of secretory (non-obstructive) azoospermia. The clinical condition is more complex in that thirty-eight percent of azoospermic patients with germ cell aplasia that had other associated major medical illnesses, i.e., hypospadias, cryptorchidism as well as elevated serum FSH (2). We reported

in an earlier study about the importance of Ad spermatogonia for insuring fertility in cryptorchidism (3). The incidence of Ad spermatogonia was assessed in 20 former cryptorchid patients, all of whom had a successful orchidopexy in childhood but developed secretory azoospermia following puberty.

MATERIALS AND METHODS

Nine percent (20/231) of patients that had a semen analysis following successful orchidopexy,

developed azoospermia. During the surgery for undescended testis, testicular biopsies were performed, fixed in glutaraldehyde and embedded in Epon. Semi-thin sections [1μ thick] were analyzed with a light microscope. The patients were classified into two groups according to the time of surgery: A: < 21 months of age ($n = 5$, mean = 10.7 ± 8.6 months) and B: during childhood, $n = 15$ mean: 10.1 ± 3 years. Nine of the 20 patients (45%) had bilateral cryptorchidism: A = 1 and B = 8. The number of Ad spermatogonia and entire number of germ cells was determined. The germ cell count was determined per tubular cross section analyzing the entire biopsy; at least 100 tubular cross-sections per biopsy. Semen analysis was performed with computer-aid and confirmed additionally with repeated microscopic examinations. At least, two semen analyses were analyzed. All patients had a comprehensive clinical examination, including a detailed history and physical examination. A total of 20 former cryptorchid patients had clinically non-obstructive azoospermia. Fifteen of the 20 patients were non-responders to HCG treatment before surgery. None of the patients at the time of the surgery had vas deferens obstructions or complete lack of the epididymis. The Wilcoxon-Mann-Whitney-U test was used for statistical analyses. The Institutional Review Board (IRB) approved all aspects of this study, according to the Helsinki declaration.

RESULTS

Nine of the 20 patients (45%) had bilateral cryptorchidism: one patient in Group A and eight patients in Group B. Both testes of all patients were located in the scrotum following puberty. Sperm count in all samples obtained was zero, confirming azoospermia. None of the patients had a completely atrophied orchidopexied testis. All patients in Group A at the time of surgery had testicular germ cells. However, the number (mean = 1.04 ± 1.4) was below the normal range for this age-group. Germ cells were absent in only 6 patients in Group B (40%) at the time of the surgery; whenever present, the number of germ cells per tubular cross-section (mean = 0.17 ± 0.4) was significantly lower if compared to Group A (patients with orchidopexy younger than

21 months of age). Ad spermatogonia were absent in the entire study population. Leydig cells of all patients were atrophic and their testicular interstitium was markedly collagenous. Plasma FSH was abnormal in 80% (16/20) of the patients, median value: 16.35 IU/L (IQR 9.075-27.85 95% CI, 3-53) while plasma testosterone of all the patients was within the normal range (FSH: 2.1 - 5.5 IU/L, T: 8.4-28.7 nmol/L).

DISCUSSION

Genetic abnormalities were present in 29% of a study population of 100 azoospermic men; azoospermia was induced in 22% of them by disease or an external influence. Cryptorchidism caused azoospermia in 27% of the population (4). Thus; cryptorchidism represents one of the most common etiologic factors of azoospermia.

Testicular malposition when untreated has a deleterious effect upon testicular development (5). Eighty-nine percent of patients with bilateral cryptorchidism who were untreated developed azoospermia, while azoospermia occurred in only 32% of those who responded successfully to hormonal [HCG] treatment and in 46% of those having had orchidopexy. However, no changes in the incidence of azoospermia (13%) were found in unilateral cryptorchid patients regardless of the treatment modalities (5). This indicates that, at least, in unilateral cryptorchid patients, azoospermia is induced by factors unrelated to the malposition. One explanation for azoospermia could be the DAZ (deleted in azoospermia) gene alteration. The DAZ gene family on the Y-chromosome long arm is the major candidate for AZFc (azoospermia factor c) phenotype of male infertility, and it is expressed only in germ cells (6). The Sertoli cell function is not altered in patients with AZFc-DAZ deletions and a strong reduction of germ cells does not affect FSH-inhibin B feedback loop (6). However, microdeletion of Yq without differences in localization of deletion was evident in cryptorchid patients and in those with idiopathic infertility (7). Therefore, Yq microdeletion patterns do not elucidate clear differences in localization and extent of deletion between

idiopathic and cryptorchid patients or between azoospermic and severely oligospermic. Furthermore, the incidence of such lesions varies considerably between 6.7 - 27.5% in unilateral ex cryptorchid patients (7).

An alternative explanation for inducing azoospermia is the absent transformation into Ad spermatogonia during mini-puberty (8). Ad spermatogonia are scarce in the first month of life; they increased markedly after 5 month of age paralleling the surge of gonadotrophins and testosterone (9). The number of Ad spermatogonia in the infant cryptorchid testes is low and there are distinctly fewer of them in the scrotal testes of unilateral cryptorchid infants compared to the control population (9). Our large fertility study showed no age related differences in the group of ex cryptorchid patients having defective germ cell development (no Ad spermatogonia) indicating that in these patients successful surgery is insufficient to prevent the development of infertility (10). One hundred and twenty two out of 231 (53%) ex cryptorchid patients had no germ cells at the time of orchidopexy (10). Importance of testosterone for Ad spermatogonia development follows from study of patients with complete androgen insensitivity (11). In these patients, receptor failure is responsive for defective transformation of Ad spermatogonia which results in azoospermia development (11). In addition, thirty-five percent of all cryptorchid boys studied did not responded to HCG treatment (8). These data suggest that in nonresponders, Leydig cell insufficiency may affect the contralateral testes in some patients with unilateral cryptorchidism; importantly, the response is due to insufficient stimulation and it is not the direct consequence of malposition of the gonads. Thus, the transformation of gonocytes into Ad spermatogonia is gonadotrophin and T dependent (8). Therefore, an early developmental arrest of Ad spermatogonia induced through gonadotrophin deficiency can lead to azoospermia.

CONCLUSIONS

These observations underscore the importance of the development of Ad spermatogonia that

takes place during mini-puberty. The non-obstructive azoospermia in cryptorchidism does not develop because of congenital lack or aplasia of germ cells, and the most severe form of infertility in cryptorchid patients cannot be prevented by an early successful orchidopexy.

CONFLICT OF INTEREST

None declared.

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Correspondence address:

Dr. Faruk Hadziselimovic
KTK-Kindertagesklinik
Oristalstrasse 87a
CH-4410 Liestal, Switzerland
E-mail: faruk@magnet.ch

Ureteral Calcinosis in Juvenile Dermatomyositis. Successful Precocious Surgical Management

Ricardo J. Duarte, Francisco T. Denes, Adriana M. Sallum

Divisions of Urology and Rheumatology, University of Sao Paulo Medical School, USP, Sao Paulo, Brazil

ABSTRACT

We report a successful surgical intervention to repair bilateral ureteral strictures in a child with juvenile dermatomyositis (JDM) and ureteral calcinosis. This is the fourth reported case in medical literature. A 9-year-old-girl with severe JDM, a rare connective tissue disease characterized by skin and muscles vasculitis, was under immunosuppressive therapy. In the course of the disease, she presented recurrent urinary tract infections. Bilateral ureteral dilation was detected by ultrasound (US) and intravenous pyelogram (IVP). CT scan showed bilateral ureteral calculus. Ureteroscopy revealed bilateral ureteral calcinosis, confirmed by histopathological analysis. Bilateral double-J stents were placed, resulting in transient improvement of ureteral dilation and infection, but only the surgical removal of abnormal ureteral portions was successful. In conclusion, endourological approach is recommended for diagnosis of urinary tract involvement by JDM because radiological evaluation can be misleading. The immunosuppressive treatment and the resection of damaged ureteral segments have allowed the control of urinary complications.

Key words: *ureter; calcinosis; dermatomyositis; ureteroscopy*
Int Braz J Urol. 2006; 32: 574-7

INTRODUCTION

Urinary tract involvement in juvenile dermatomyositis (JDM) is an uncommon and challenging disease to treat. We report the first case with no surgical complications and successful outcome.

CASE REPORT

A 9-year-old girl with JDM, receiving prednisone, cyclosporine-A and methotrexate, presented recurrent urinary tract infections and

bilateral pieloureteral dilation in ultrasonography. IVP revealed a radiopaque left upper ureteral lesion and bilateral ureteral dilation near the iliac vessels with distal obstruction, more evident at the right side. A computed tomography (CT) scan diagnosed a left upper and mid ureteral calculus, and another in the right mid ureter (Figure-1).

The child was first submitted to a right side ureteroscopy, because it was the most dilated side. It revealed no calculus in the lumen, but the ureteral wall showed calcifications. Biopsy showed an inflammatory process with dystrophic calcifications and mucosal ulceration (Figure-2).

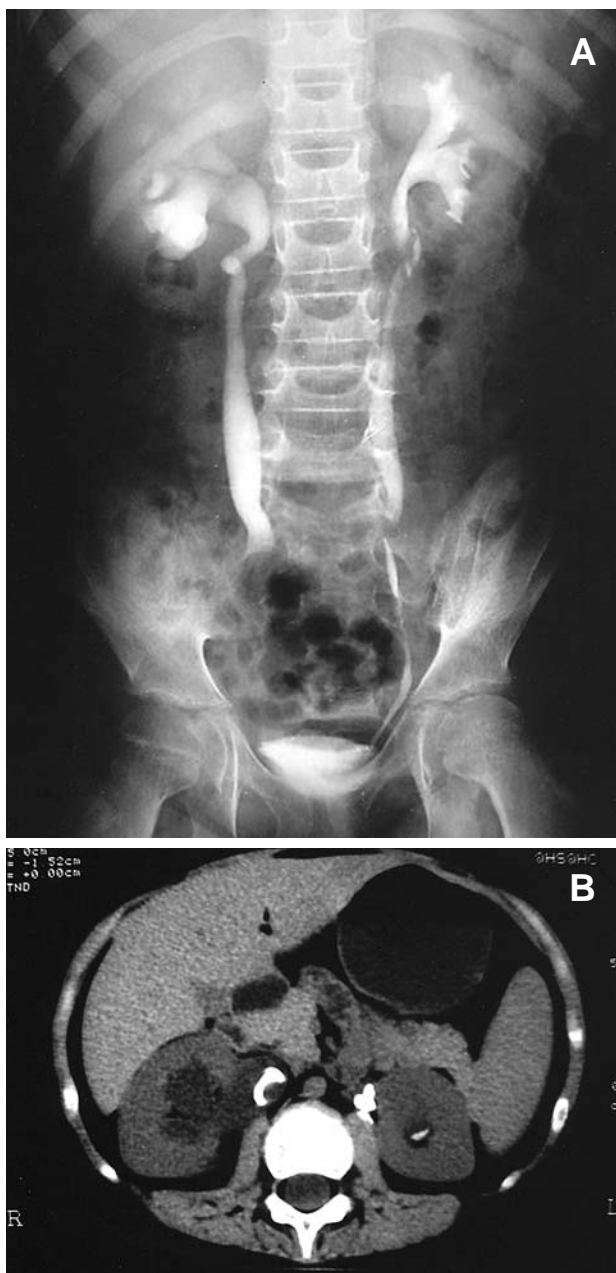


Figure 1 – Juvenile dermatomyositis. A) Preoperative intravenous pyelogram revealing bilateral ureteral dilation. B) Preoperative CT scan showing bilateral “ureteral calculus”, misdiagnosing ureteral calcification.

Bilateral double-J stents were placed improving ureteral dilation. Periodical substitution of the stents was scheduled, but the replacement of the

left stent was not possible due to non-progression of the guide wire. Surgery was then indicated (left subcostal lombotomy). The left upper ureter was calcified and attached to the psoas muscle. A 2 cm calcified segment was then removed followed by termino-terminal anastomosis and double-J placement. The left mid segment and the right ureter were untouched since they were considered satisfactorily pervious and a conservative management was chosen. Histopathological findings were similar to previous biopsy.

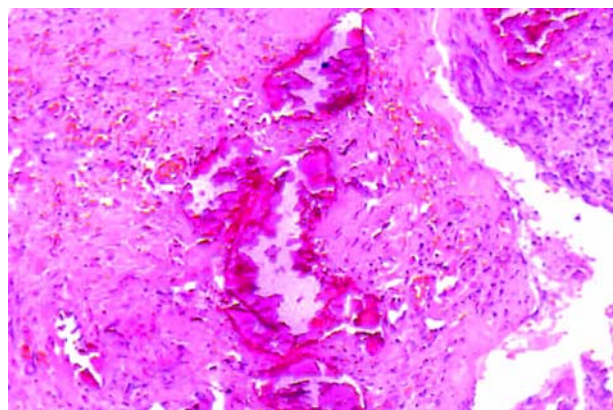


Figure 2 – Microscopy of removed ureter. Note inflammatory infiltrate involving the ureteral muscular wall with widespread calcifications (HE, X100).

Two months later, a 2 cm calcified segment of the lower right ureter was resected near the iliac vessels and a termino-terminal anastomosis was performed through a right extended infraumbilical transverse incision. The left stent was then removed and, after a retrograde ureteropyelogram, we considered the left ureter pervious and decided to keep it under observation. Chronic ureteritis with urothelial hyperplasia and fibrous thickness of mucosa and submucosa were observed in the removed portion.

The child did well, without urinary tract infections, dilation or complications. Postoperative IVP and CT scan (Figure-3) revealed a slight left ureteral enlargement without clinical implications and small calcification in the left psoas muscle.

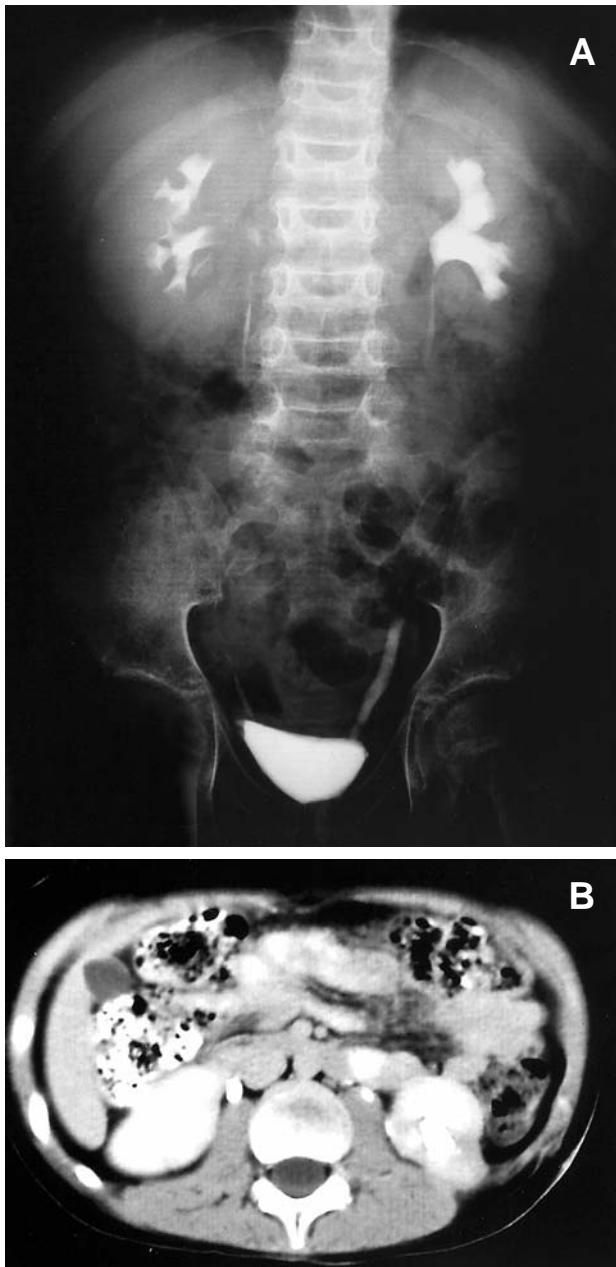


Figure 3 – Juvenile dermatomyositis. A) Postoperative intravenous pyelogram revealing satisfactory urinary flow without ureteral dilation. B) Postoperative CT scan revealing a small calcification in the left psoas muscle and left ureter, without dilation.

DISCUSSION

Urinary tract involvement in JDM is rarely reported. Borrelli et al. (1) have described a child with

JDM and bilateral ureteral necrosis, with bad evolution and death due to the disease. Bléry et al. (2) and Le Guillou et al. (3) have reported the same situation, with surgical complications such as stenosis and fistula.

Considering that JDM is an inflammatory process, the early introduction of immunosuppressive agents and control of the disease, associated to a careful periodic urological evaluation and precocious surgical treatment, have resulted in the successful outcome of our patient.

The image methods misdiagnosed lithiasis. Only ureteroscopy and ureteral biopsy disclosed the diagnosis of calcinosis. Although radiological evaluation was suggestive of lithiasis, it was a good decision not to insist with endourological procedures. Surgical resection of the damaged segment was efficient, with normalization of urinary flow without complications.

CONCLUSION

Children with JDM and recurrent fever should be submitted to urinary tract evaluation, but the image methods can be unclear. In this case, ureteroscopy disclosed the diagnosis, but did not solve the problem. Precocious resection of the damaged ureteral segments has improved the obstructive problem and allowed urinary tract infection control. These remarks can be useful to the management of similar cases.

CONFLICT OF INTEREST

None declared.

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Correspondence address:

Dr. Ricardo Jordão Duarte
Rua Afonso Brás 525 / 82
04511-011, São Paulo, SP, Brazil
E-mail: ricjordao@uol.com.br

An Exploration into Patient Preference for Injectable Therapy over Surgery in the Treatment of Female Urinary Incontinence

Steven P. Petrou, Scott W. Lisson, Julia E. Crook, Deborah J. Lightner

Department of Urology (SPP) and Biostatistics Unit (SWL) Mayo Clinic, Jacksonville, Florida and Department of Urology (JEC, DJL) Mayo Clinic, Rochester, Minnesota, USA

ABSTRACT

Objective: To explore patient preference for injectable therapy over open surgery in the treatment of urinary incontinence.

Material and Methods: Fifty-eight female patients presented for treatment of urinary incontinence. During the initial interview process, they were asked to quantify their preference for injectable therapy over surgery by specifying the lowest success rate they would accept and still try injectable therapy. The results were summarized and assessed in relation to patient age and history of previous urogynecologic surgery.

Results: The mean lowest acceptable success rate for all 58 surveyed patients was 34%, with 23 (40%) accepting a success rate of only 10%. Although not statistically significant, the data suggested that older patients may tend to accept lower success rates than younger patients (mean of 39% for patients aged less than 60 years compared to 22% for those aged 80 years or older). There was no difference in response based on history of previous urogynecologic surgery.

Conclusion: Patients appear willing to accept a relatively low success rate for injectable therapy compared to open surgery.

Key words: urinary incontinence, stress; injections; patient preference; survey

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INTRODUCTION

The treatment of female stress urinary incontinence includes multiple appropriate options ranging from pelvic floor rehabilitation to open surgical procedures. However, it is intuitive that patients will choose a less invasive treatment to minimize their convalescence. This explains the appeal of periurethral bulking agents. Unfortunately, the success rates of injectable therapies have been less than those obtained with surgical procedures (1,2). Nevertheless, a common perception is that patients, if offered injectable agents, will continue to be interested in this option and will be accepting its lower success rate. We attempted to explore this

thought and to quantify the success rate of injectable therapy with a bulking agent that patients would consider acceptable.

MATERIALS AND METHODS

We interviewed 58 successive incontinent female patients newly presenting to the Department of Urology during a 6-month period. The patients were asked the following question orally by the attending urologist: "If it is determined that you may benefit from either surgical therapy, which is approximately 90% successful but requires postoperative convalescence, or an injectable therapy with a minimal postoperative convalescence, what is the

lowest success rate that you would accept and still try injectable therapy with an unspecified agent?" If patients had queries regarding the injectable therapy or surgery, every effort was made to respond in an unbiased and nonpersuasive manner. It was intimated that both procedures would be completed under general anesthesia. At the time of the questioning, the patients had not been categorized as having stress urinary incontinence, urinary urge incontinence, overactive bladder symptoms, or mixed urinary incontinence. Furthermore, patients were queried near the beginning of their consultation in order to limit potential physician bias and evaluation impact. The patients were asked to respond in increments of 10% success rates, ranging from 0% to 100% (i.e., a 10% success rate, a 20% success rate, etc.).

Wilcoxon's rank sum test was used to compare responses between patients with and without previous urogynecologic surgery, and Spearman's rank correlation test was used to investigate a possible association with age. The Institutional Review Board approved this study.

RESULTS

The patients' mean age was 70 years (range: 31-95 years). Eighteen patients (31%) had previous anti-incontinence or prolapse repairs: injectable therapy with carbon-coated zirconium oxide beads (2 cases), injectable therapy with collagen (3 cases), pubovaginal sling with autologous fascia (3 cases), suburethral sling with non-autologous material (1 case), Burch colposuspension (1 case), Marshall-Marchetti-Krantz urethropexy (2 cases), and pelvic prolapse surgery (6 cases).

The mean lowest acceptable success rate was 34%. Twenty-three of the 58 patients (40%) would accept a success rate of 20% or less and still undergo the minimally invasive procedure, whereas another 40% would require a success rate of 50% or greater. There was no evidence of any tendency for different responses in patients with a history of previous anti-incontinence procedure or pelvic prolapse surgery compared to those without ($P = 0.54$). Although not statistically significant, the data suggested that older

patients may have a tendency to accept lower rates than younger patients (Spearman's rank correlation: -0.23 ; $P = 0.08$). The patient responses are displayed in Figure-1, by age and by history of previous surgery. Mean lowest acceptable success rates by age group were 39%, 38%, 35% and 22% for ages < 60 , 60-69, 70-79 and 80 + years respectively.

Five of the 58 patients had prior experience with bulking agents. Three (two aged 79, one aged 75) had experience with injectable collagen and indicated that their lowest acceptable success rates were 10%, 30%, and 30%. The other two (aged 50 and 68) had experience with Durasphere injectable bulking agent (Advanced UroScience, Inc, St. Paul, Minnesota); their lowest acceptable success rate was 50%. These data provide no suggestion that patients with prior experience with injectable bulking agents differed in their preference levels from those without, but in view of the small numbers, no valid conclusion can be made from this sample.

COMMENTS

None of the available bulking agents, including bovine cross-linked collagen and carbon beads, have duplicated the success rates obtained with open anti-incontinence surgical procedures (1,3). However, injectable therapy has an inherent attractiveness, given its minimally invasive nature, ease of administration, and acceptable short-term results. Hence, injectable treatments continue to be offered either as first line or second line therapies or as the only medically tolerable procedure for patients who are infirm or fearful of surgery (3,4). Bulking agents are decried for their lack of comparable success rates, but the trade-off for the patient has been studied little.

Our results from this early exploratory study suggest that many patients are likely to accept a vastly lower success rate for injectable therapy over a more morbid open surgical procedure; for example, 19 of the 58 patients (33%) were willing to accept only a 10% chance of success (Figure-1). Although this result is initially surprising, it parallels the findings by Robinson et al. (5), who examined what

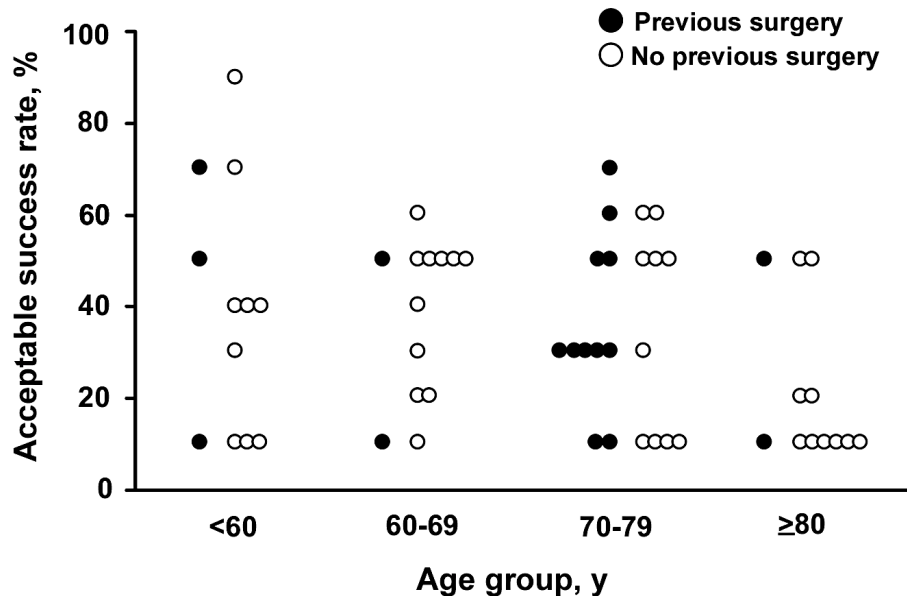


Figure 1 – Patients' lowest acceptable success rates for injectable therapy among 58 patients with or without a history of previous urogynecologic surgery. The patients provided these rates in response to an initial interview question during evaluation for urinary incontinence.

women perceive as a cure and, as we did in the present study, assessed patient tolerability of loss of efficacy if coupled with a reduction in morbidity. Those authors found that 38% of the women surveyed were willing to accept a minor operation if there was an 85% chance of a cure and that 57% would tolerate a 60% improvement rate if the intervention was only a clinical procedure (5). In addition, Karantanis et al. (6), in a study that analyzed women's preferences for treatment of stress urinary incontinence, noted that 66% of the women preferred pelvic floor treatment, 24% chose the tension-free vaginal tape (TVT) procedure, and 9% desired open colposuspension. Although Karantanis et al. did not include injectable therapy as a treatment option, their findings of a strong patient preference for less invasive therapies must be given an enhanced consideration in view that they used carefully written explanations and instructions to minimize potential bias. These findings above mirrored our conclusions that many patients prefer a minor procedure with a lower risk of complications but are also content to

accept the accompanying trade-off of a lower success rate (5,6).

During the interview process, the study question was kept deliberately generic with regard to the specific injectable substance in order to eliminate potential patient bias based on experience or knowledge. Although the method of questioning did not involve a validated instrument, the query was simple, to the point, and suitable for an early exploration into this topic. In addition, we did not select patients to include or exclude based on type of incontinence because we wanted to explore general preference for therapies; after evaluation and surgical selection, the population would potentially be biased and possibly less representative of the unadulterated general population. The refining of the study group by evaluating first and asking second is a compelling idea, but we chose the alternative to avoid potential instillation of bias by the attending urologist concerning case specific therapeutic options. A potential weakness of the study is that the query was oral. A written form with descriptive and question

portions would have possibly limited potential bias even further.

Patients' perception of injection therapy as being nonsurgical may influence these results. This distinction between injection and operative procedures may be blurred and difficult to accept for a surgeon seeking an efficient end to a course of care; consequently, while reviewing options with the patient, a surgeon may present an unrecognized bias toward operative repair because of the current remarkable rapidity with which newer sling procedures are performed as opposed to the injectable therapeutic pathway that might entail repeated visits, injections, and ultimately an operative procedure in a moderate percentage of patients. A patient's preference should be understood as potentially different from the surgeon's. Robinson et al. (5) noted that only 23% of their study group found a major operation acceptable, even one that had an 85% cure rate, whereas Karantanis et al. (6) found that the women they studied preferred a TVT procedure over an open colposuspension by nearly 3 to 1.

If one accepts the tenet that few patients really want to have an elective surgical procedure, one may embrace injectable therapy as a definite step in the treatment of incontinence, regardless of success rates. Surgeons often abandon a procedure that is not perceived as being overly successful. However, perhaps instead of avoiding injectable therapy because of perceived ineffectiveness and potential inefficiency, one should remember the high degree of patient acceptance for an intervention that requires essentially no effort or assumed risk on the part of the patient. It will be of great future interest to see if these initial findings are mirrored in a large sample study in other voiding dysfunction studies, such as those involving diet and overactive bladder (7).

Although this exploration has concluded, it did alert us to the great preference of patients for therapies that are not surgical and piqued our interest into further inquiries of a similar nature. It may be of value to perform a study in the same manner as Karantanis et al. (6) to stratify patient preference for degrees of invasiveness, such as among injectable therapy, transobturator technique, and autologous

fascial sling, and the reasons for same. We are currently in the early stages of formulating a written questionnaire to quantify patient preference in the reciprocal situation: how high a success rate has to be for a patient to choose an invasive operation. Although the permutations and criticisms of this question will be inspiring (i.e., minimally invasive vs. open surgery, transobturator vs. pubovaginal), the results will assist the entire field in the development of newer techniques and technologies.

CONCLUSION

Many patients are likely to accept a markedly lower rate of success with injectable therapy than with open surgery. There is no evidence that age and previous operative failure have a clinically significant effect on patients' desire to prefer injections. Injectable therapy is an option that is attractive to patients, as evidenced by their willingness to accept this form of treatment despite its potentially extremely low success rate.

CONFLICT OF INTEREST

None declared.

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Correspondence address:

Dr. Steven P. Petrou
Department of Urology, Mayo Clinic
4500 San Pablo Road
Jacksonville, FL 32224, USA
Fax: + 1 904 953-2218
E-mail: petrou.steven@mayo.edu

Development of a Urinary Lithiasis Localizer Mechanism to Couple Ultrasound and Extracorporeal Lithotripsy Equipment in Canine Model

Enrico Andrade, Gustavo Alarcon, Eduardo Pompeu, Archimedes Nardoza Jr, Joaquim A. Claro, Valdemar Ortiz, Miguel Srougi

Department of Urology, Paulista School of Medicine, UNIFESP and Biotery, Faculty of Medicine, University of Sao Paulo, USP, Sao Paulo, Brazil

ABSTRACT

Introduction: Due to the evolution of extracorporeal lithotripsy equipment (ESWL) and presently, the fact that most part of the equipment does not present ultrasound to localize urinary calculi, a system that allows adapting ultrasound equipment to ESWL equipment was developed, disposing only of fluoroscopy. Thus, this equipment was developed and was tested in urinary stones in canine models, to check its precision in relation to fluoroscopy.

Method: Seven male dogs were utilized with the introduction, in the bladder through the ureteral route, of chalkstones, with initial localization by fluoroscopy, with a further ultrasound coincidence check localization of the vesical stones, being submitted to ESWL with a 3-hour, 21 days and 60 days follow-up after the procedure.

Results: Success of localization in all animals was verified presenting elimination of stones in the first micturitions, after ESWL. No complications were verified in those animals for 60 days.

Conclusion: We verified that this equipment can lead to an update of the equipment that use only fluoroscopy, increasing in this way, their technical capacity in the treatment of urinary calculi, mainly in cases of non-radiopaque stones.

Key words: urolithiasis; bladder; lithotripsy; ultrasonography; animal models; dogs

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INTRODUCTION

After its introduction in 1980, extracorporeal shockwave lithotripsy (ESWL) dramatically changed the direction of the treatment of urolithiasis.

Extracorporeal lithotripsy is a procedure in which urinary tract stones are pulverized in small fragments through shockwaves. Those fragments can be spontaneously eliminated.

This non-invasive procedure allows patients to be treated without the need for a surgical intervention or an endoscopic procedure.

All ESWL machines consist of the following elements: 1) a shockwave generator, 2) a shockwave focusing system, 3) a urinary stone imaging or localization system, 4) a patient coupling mechanism (1,2).

Shockwave generator - All generators are based on the geometric principle of an ellipse. Shockwaves are created in the first focal point of the ellipsoid (F1 – at the ellipse center), are directed to the second focal point (F2), inside the patient. The focal zone at the F2 area, is the place where there is a maximum concentration of the shockwaves. There are three types of generators to produce shockwaves: electrohydraulic, piezoelectric and electromagnetic (Figure-1).

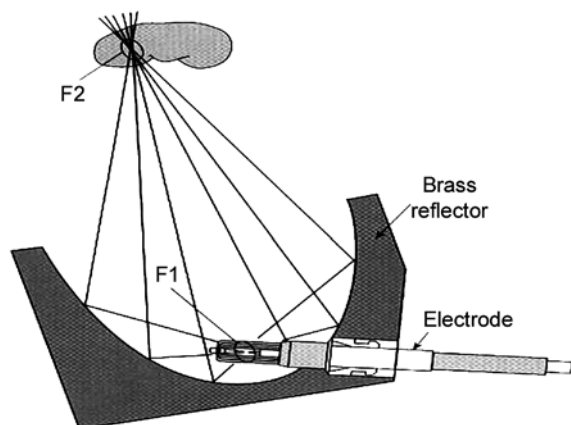


Figure 1 – Shockwave focus system.

Shockwave focusing system - All the machines require a focusing system to align, direct and concentrate the energy produced at point F2 (at the stone).

Urinary stone imaging or localization system - Visualization and localization of urinary stones are used to position the stone at F2 point. Fluoroscopy and ultrasound can be used to localize the stone.

Fluoroscopy advantages are stone visualization in all the urinary tract, familiarity and ability of the urologist with the technique, possibility of using ionized contrasts and checking of anatomic details. Disadvantages are utilization of ionizing radiation, visualization of radiotransparent stones and high cost of the equipment, installation and maintenance.

Ultrasonography was initially developed to help multifunctional lithotripsy equipment where both urinary and bile stones were treated. Presently, it is used in different equipment for its lower cost and easy maintenance, when compared to those that use fluoroscopy. Advantages are visualization of radiopaque and radiotransparent stones, real time monitoring of the procedure without ionizing radiation. Despite those big advantages, there are important disadvantages: ability of the operator with the ultrasound and stones in urinary tract mid and lower ureter.

In truth, large medical centers possess new equipments that have both localization technologies

such as ultrasound and fluoroscopy, despite the higher cost for the acquisition of such equipment, the option for fluoroscopy is that it can be used in other urologic endoscopic procedures. Also, there use to be a disadvantage since there was no training of the urologist for the use of ultrasound. That is not the case nowadays, since the majority of the urologists are entirely familiar with ultrasound (3-5).

Thus, the development of this equipment aims at the modernization of already existing lithotripsy equipment in use such as Breakstone, Macstone, Medstone, Econolith and Lithomax; and they can be adapted to any 7.5 MHz probe of the most different ultrasound equipment models, either convex or linear, together with fluoroscopy of the original equipment. Such equipment would be updated and become more competitive with new equipment that holds both localization and calculation technologies.

MATERIALS AND METHODS

A mechanized system was developed for the ultrasound 7.5 MHz linear probe Hitachi EUB300®, to the lithotripsy equipment, with appropriate angulation so that the ultrasound probe keep a wave emission line passing through the F2 point. With mathematical and geometric formulas, the distance from the probe to the F2 point was calculated and thus, the ultrasound equipment was gauged to focus the equipment's virtual focal point, with a diameter of 5 mm (the ultrasound equipment focal point is standardized in 5 mm), as already being the F2 point.

This system consists of 3 parts: 1) ESWL machine fixing system; 2) angulation and distance system of the F2 focal point and 3) ultrasound probe adapting and fixing system (Figure-2).

Thus, through the animal model with 7 male breadless medium size dogs supplied by the Biotery of the Faculty of Medicine of São Paulo. Anesthetized they were submitted to two 10 mm diameter cylindrical stones, chalk – dehydrated calcarean gipste in the bladder by ureteral catheterization, to deposit intravesical stones, all animals have received doses of prophylactic antibiotic therapy, according to the vet's guidance (6-8).



Figure 2 – Ultrasound probe adaptation and fixing system.

Initially the ESWL equipment (Breakstone, Inc) was adjusted to focus through the X-RAY fluoroscopy system (original from the lithotripsy equipment) and afterwards, the ultrasound probe was brought near the animal to verify the correspondence of the focus (stone).

After being focused the extracorporeal lithotripsy was performed for the fragmentation of those stones with 12 Kv energy, 2000 shoots and real-time follow-up of calculi fragmentation, 3 hours after the procedure and 21 days after with the new vesical and urethral ultrasound. We have also observed urethral obstruction in the animals, by fragment of the stones that could obstruct the urethra at the point of the canine urethra where the penile canine bone is located.

RESULTS

Mean dog weight was 13.64 kg. The procedure with the introduction of the stones and the lithotripsy had a mean duration of 72 minutes, with the performance of 2000 shoots per animal. Fragmentation of all stones and the elimination of the stones in the first micturitions of the animals were obtained, being confirmed with vesical ultrasound in the third hour after the end of the procedure (Figures-3 and 4). New ultrasounds were taken after 21 days to confirm the complete elimination of fragments.

Those animals were clinically followed for 60 days and no complications occurred such as urinary obstruction or infection (Table-1).

COMMENTS

Presently the efficiency of new extracorporeal lithotripsy machines have been little improved in relation to the first ESWL machine (HM3), thus,

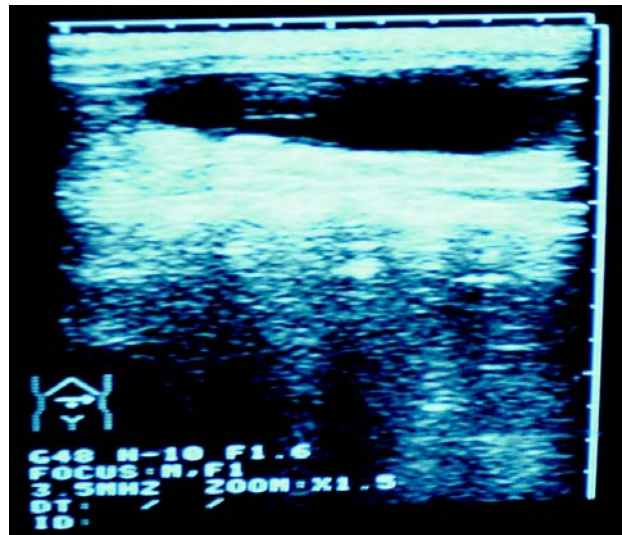


Figure 3 – Canine vesical stone, pre extracorporeal lithotripsy.

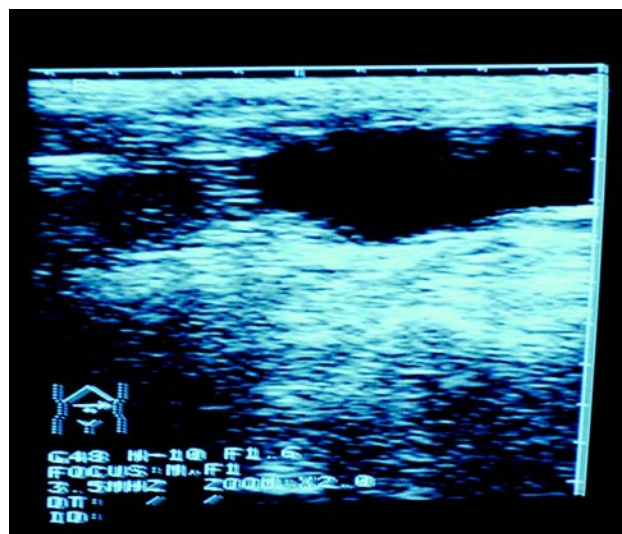


Figure 4 – Canine vesical stone, post extracorporeal lithotripsy.

Table 1 – List of animals with localization, fragmentation and complications.

Dogs	Weight (Kg)	Coinciding Localization X-ray and Ultrasound	Fragmentation	Complications
1	12.0	yes	yes	no
2	14.3	yes	yes	no
3	11.8	yes	yes	no
4	14.1	yes	yes	no
5	12.7	yes	yes	no
6	15.9	yes	yes	no
7	14.7	yes	yes	no

the improvement of the fragmentation method is due to the technical improvement of stone localization by ultrasound. By using the ultrasound, renal stones can be more precisely identified, mainly when some indexes are taken into consideration: 1) Stone size; 2) Radiotransparency; 3) Need of use of a radiological contrast; 4) Cost of the equipment and maintenance.

However, mid and inferior ureter calculi are better treated with endoscopic procedures and many calculi are not directed to the ESWL procedure for they cannot be visualized by the X-ray in the kidneys, due to their size. Thus, we can increase the percentage of those patients that are not treated by ESWL and reduce the number of risks of growth of those stones or the spontaneous elimination of larger stones that might substitute the ureter and provoke the need of an urgent endoscopic surgery.

Presently, many urologists have acquired training and have improved urologic ultrasound technique, and that is an advantage to the method of localization by ultrasonography.

Verifying the financial factor, there are great advantages, such as reduction of operational costs of approximately 60% due to various factors: 1) modernization of lithotripsy equipment without the need to change old models for new ones; 2) economy with radiation protection for procedure rooms; 3) increase of the number of cases due to radiotransparent stones; 4) decrease of costs with drugs for the contrast of the urinary tract; 5) reduction of the electric energy of fluoroscopy.

CONCLUSION

In this way, the modernization of the equipment would lead to a technical improvement and decrease of operational costs of the equipment, since initially there would be a decrease with the maintenance of fluoroscopy equipment, without the need of changing the lithotripsy equipment for a more recent model and there would be only the need to install this equipment to adapt an ultrasound.

CONFLICT OF INTEREST

None declared.

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Correspondence address:

Dr. Enrico Andrade
Rua Tijuco Preto, 845 / 42
São Paulo, SP, 03316-000, Brazil
Fax: + 55 11 6197-0317
E-mail: enricoandrade@uol.com.br

UROLOGICAL SURVEY

Francisco J.B. Sampaio
Urogenital Research Unit
State University of Rio de Janeiro

Athanase Billis
State University of Campinas
Campinas, SP, Brazil

Andreas Böhle
Helios Agnes Karll Hospital
Bad Schwartau, Germany

Steven B. Brandes
Washington University in St. Louis
St. Louis, Missouri, USA

Fernando J. Kim
Univ Colorado Health Sci Ctr
Denver, Colorado, USA

Barry A. Kogan
Albany Medical College
Albany, New York, USA

Manoj Monga
University of Minnesota
Edina, MN, USA

Steven P. Petrou
Mayo Medical School
Jacksonville, Florida, USA

Adilson Prando
Vera Cruz Hospital
Campinas, SP, Brazil

Arnulf Stenzl
University of Tuenbingen
Tuebingen, Germany

STONE DISEASE

Renal Stone Epidemiology in Rochester, Minnesota: An Update

Lieske JC, Pena de la Vega LS, Slezak JM, Bergstralh EJ, Leibson CL, Ho KL, Gettman MT

Department of Internal Medicine, Division of Nephrology and Hypertension, Mayo Clinic, Rochester, Minnesota, USA

Kidney Int. 2006; 69: 760-4

Studies in Western countries have suggested an increasing incidence of nephrolithiasis (NL) in the latter part of the 20th century. Therefore, we updated NL epidemiology data for the Rochester population over the years 1970-2000. All Rochester residents with any diagnostic code that could be linked to NL in the years of 1970, 1980, 1990, and 2000 were identified, and the records reviewed to determine if they met the criteria for a symptomatic kidney stone as defined in a previous Rochester, MN study. Age-adjusted incidence (+/-s.e.) of new onset symptomatic stone disease for men was 155.1 (+/-28.5) and 105.0 (+/-16.8) per 100,000 per year in 1970 and 2000, respectively. For women, the corresponding rates were 43.2 (+/-14.0) and 68.4 (+/-12.3) per 100,000 per year, respectively. On average, rates for women increased by about 1.9% per year (P=0.064), whereas rates for men declined by 1.7% per year (P=0.019). The overall man to woman ratio decreased from 3.1 to 1.3 during the 30 years (P=0.006). Incident stone rates were highest for men aged 60-69 years, whereas for women, they plateaued after age 30. Therefore, since 1970 overall NL incidence rates in Rochester have remained relatively flat. However, NL rates for men have declined, whereas rates for women appear to be increasing. The reasons remain to be determined.

Editorial Comment

Though most recent studies suggest an increase in the incidence of nephrolithiasis, attributed to dietary and lifestyle changes, this interesting study suggests the contrary. An increase in incidence in females is balanced by a decrease in incidence in males, leading to a flat incidence rate when compared to 30 years ago.

The authors note that affluence and dietary factors associated with higher socioeconomic status have been implicated as risk factors for stone disease. It would be important therefore to evaluate any changes in the socioeconomic status of their study group; for example has the average income, unemployment rate, average education etc. remained stable during this time period? The intriguing question remains what has changed in men from 1980 onwards that has dramatically decreased the incidence of stone disease? What has changed in women from 1970 onwards that has resulted in a dramatic increase in stone disease? Is it dietary, hormonal, environmental, iatrogenic (increased use of oral contraceptives, calcium supplements, or other agents)? The authors reported only the incidence of symptomatic stones, though they did extract all stones including those detected incidentally by high-resolution imaging technologies. It would be interesting for the investigators to report these numbers also, so as to predict the increased volume of patients being referred for prophylactic surgical and medical therapy.

Dr. Manoj Monga*Professor, Department of Urology
University of Minnesota
Edina, Minnesota, USA*

Type 2 Diabetes Increases the Risk for Uric Acid Stones

Daudon M, Traxer O, Conort P, Lacour B, Jungers P

Assistance Publique-Hopitaux de Paris, Laboratoire de Biochimie A, Hopital Necker-Enfants Malades, Paris, France

J Am Soc Nephrol. 2006; 17: 2026-33

An increased prevalence of nephrolithiasis has been reported in patients with diabetes. Because insulin resistance, characteristic of the metabolic syndrome and type 2 diabetes, results in lower urine pH through impaired kidney ammoniogenesis and because a low urine pH is the main factor of uric acid (UA) stone formation, it was hypothesized that type 2 diabetes should favor the formation of UA stones. Therefore, the distribution of the main stone components was analyzed in a series of 2464 calculi from 272 (11%) patients with type 2 diabetes and 2192 without type 2 diabetes. The proportion of UA stones was 35.7% in patients with type 2 diabetes and 11.3% in patients without type 2 diabetes ($P < 0.0001$). Reciprocally, the proportion of patients with type 2 diabetes was significantly higher among UA than among calcium stone formers (27.8 versus 6.9%; $P < 0.0001$). Stepwise regression analysis identified type 2 diabetes as the strongest factor that was independently associated with the risk for UA stones (odds ratio 6.9; 95% confidence interval 5.5 to 8.8). The proper influence of type 2 diabetes was the most apparent in women and in patients in the lowest age and body mass index classes. In conclusion, in view of the strong association between type 2 diabetes and UA stone formation, it is proposed that UA nephrolithiasis may be added to the conditions that potentially are associated with insulin resistance. Accordingly, it is suggested that patients with UA stones, especially if overweight, should be screened for the presence of type 2 diabetes or components of the metabolic syndrome.

Editorial Comment

As obesity, the metabolic syndrome and type 2 diabetes increase in prevalence in the Western world, newly recognized associated morbidities continue to increase the impact on patients and healthcare. This article demonstrates a strong link between uric acid urolithiasis and type 2 diabetes. The hypothesis rests in the lower urine pH noted in type 2 diabetes predisposing to uric acid stone formation. The authors combined calcium oxalate and calcium phosphate stones into one group: "calcium-stones", though calcium oxalate stones are predisposed to formation in more acidic urine while calcium phosphate stones are predisposed to formation in more alkaline urine. A repeat analysis separating these two stone compositions may be of benefit. In the small group of patients (25) with type 2 diabetes who underwent urinary evaluations, the urine pH was comparable to patients without diabetes who formed uric acid stones, raising questions regarding the validity of the hypothesis proposed. Though the pathophysiology may not be clear, the 7-fold risk of a uric acid stone composition in type 2 diabetes suggests a strong link, and supports the recommendation that uric acid stone formers be screened for the metabolic syndrome.

Dr. Manoj Monga

*Professor, Department of Urology
University of Minnesota
Edina, Minnesota, USA*

ENDOUROLOGY & LAPAROSCOPY

Retrospective Comparison of Retroperitoneal Laparoscopic Versus Open Dismembered Pyeloplasty for Ureteropelvic Junction Obstruction

Zhang X, Li HZ, Ma X, Zheng T, Lang B, Zhang J, Fu B, Xu K, Guo XL

Department of Urology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, People's Republic of China

J Urol. 2006; 176: 1077-80

Purpose: We evaluated the clinical value of retroperitoneal laparoscopic dismembered pyeloplasty for ureteropelvic junction obstruction compared with open surgery.

Materials and methods: The clinical data of 56 patients who underwent retroperitoneal laparoscopic dismembered pyeloplasty were retrospectively compared with those of 40 patients who underwent open dismembered pyeloplasty through a retroperitoneal flank approach. The Student t test, Pearson chi-square test and Mann-Whitney rank sum test were applied for statistical analysis as appropriate.

Results: Patient demographic data were similar between the 2 groups. In the laparoscopic group operative time (80 vs 120 minutes), estimated blood loss (10 vs 150 ml), recovery of intestinal function (1 vs 2 days), analgesic requirements (diclofenac sodium suppository) (75 vs 150 mg), incision length (3.5 vs 21 cm) and postoperative hospital stay (7 vs 9 days) were better than in the open group ($p < 0.001$ for all). No intraoperative complications occurred in either group. The incidence of postoperative complications (2 of 56, 3.6% vs 3 of 40, 7.5%, $p = 0.729$) and success rates (55 of 56, 98.2% vs 39 of 40, 97.5%, $p = 0.058$) were equivalent in the 2 groups.

Conclusions: Retroperitoneal laparoscopic dismembered pyeloplasty is a minimally invasive, safe and effective therapy for ureteropelvic junction obstruction with low morbidity, shorter convalescence and excellent outcomes, and can be accomplished reasonably quickly in experienced hands.

Editorial Comment

The new era of reconstructive surgery demonstrates the evolvement of minimally invasive approaches to the Ureteropelvic junction (UPJ) repair. In a retrospective study, the authors compared the retroperitoneal laparoscopic dismembered pyeloplasty technique to the open pyeloplasty approach with comparable results and complication rates. Significant difference between both techniques included blood loss and incision length. Moreover, Dr. Winfield discussed in his editorial comment "Management of Adult Ureteropelvic Junction Obstruction - Is it Time for a New Gold Standard?" (J. Urol, 176, September 2006, 866-867) the diversity of different surgical techniques available to repair the UPJ obstruction but caution to report post-operative success should be critically evaluated: 1) objectively (nuclear renal lasix scan) and 2) subjectively (pain free post-op).

Dr. Fernando J. Kim

*Chief of Urology, Denver Health Med Ctr
Assistant Professor, Univ Colorado Health Sci Ctr
Denver, Colorado, USA*

Laparoscopic Cytoreductive Nephrectomy: The M. D. Anderson Cancer Center Experience

Matin SF, Madsen LT, Wood CG

Department of Urology, University of Texas M. D. Anderson Cancer Center, Houston, Texas, USA

Urology. 2006; 68: 528-32

Objectives: Cytoreductive nephrectomy (CN) is an integral component in treating patients with metastatic renal cell carcinoma. Critics of CN argue that perioperative morbidity or postoperative disease progression may preclude patients from receiving systemic therapy. Laparoscopic cytoreductive nephrectomy (LCN) may allow for reduced morbidity and may increase the likelihood of patients receiving systemic therapy.

Methods: From April 2001 to March 2005, 38 patients underwent LCN at our institution. We evaluated perioperative parameters such as demographics, blood loss, operative time, complications, follow-up time, interval to systemic therapy, and survival. A contemporary open cytoreductive surgery group was evaluated for comparison.

Results: The median patient age was 62 years (range 41 to 82). Most patients had a performance status of 1 or less. The median operative time was 188 minutes, and the median blood loss was 175 mL. All specimens were removed intact. The median tumor size was 8 cm (range 3.5 to 14). The median hospitalization was 3 days. Two major (5.7%) and four minor (11.4%) complications occurred, but no perioperative mortality. Postoperatively, 97.4% of patients were eligible for, or received, systemic therapy at a median of 41 days. The overall median survival was 18.1 months. In contrast to open CN, LCN resulted in decreased blood loss and hospital stay, with no differences in complications, operative time, or interval to systemic therapy.

Conclusions: LCN is a safe and effective surgical approach for select patients with metastatic renal cell carcinoma. Our results have indicated that with proper patient selection, LCN is feasible, morbidity is minimized, and systemic therapy is delivered in a timely fashion.

Editorial Comment

The new possibilities of targeted adjuvant therapy for renal cell cancer encouraged the practice of cytoreductive nephrectomy. One of the pivotal issues against this approach is the possible delay of institution of systemic therapy. With the advent of less invasive surgery, i.e.; laparoscopic cytoreductive nephrectomy, initiation of systemic therapy can be started sooner increasing the possibility of better survival.

Dr. Fernando J. Kim

*Chief of Urology, Denver Health Med Ctr
Assistant Professor, Univ Colorado Health Sci Ctr
Denver, Colorado, USA*

IMAGING

Fat Poor Renal Angiomyolipoma: Patient, Computerized Tomography and Histological Findings

Milner J, McNeil B, Alioto J, Proud K, Rubinas T, Picken M, Demos T, Turk T, Perry KT Jr.

Loyola University, Chicago, Illinois, USA

J Urol. 2006; 176: 905-9

Purpose: We reviewed our experience with fat poor cases of angiomyolipoma.

Materials and methods: The records of patients with angiomyolipoma, as determined by pathological study, from 1998 to 2004 were reviewed by recording patient demographics and outcomes. Fat poor cases were defined as the failure of imaging to demonstrate fat in a lesion. Computerized tomography and histological characteristics were assessed.

Results: Histologically confirmed angiomyolipoma was found in 15 patients. Multiple lesions were found in 3 of 15 cases (20%). Of these 15 patients who underwent surgery 11 (73%) had unsuspected angiomyolipoma

due to absent fat on computerized tomography and they underwent intervention for presumed renal cell carcinoma. Mean age +/- SD in this group was 54 +/- 15 years and 8 of 11 patients (73%) were female, of whom 4 (50%) had uterine fibroids. These lesions were found incidentally in 7 of 11 cases (64%). Operative complications developed in 2 of 11 patients (18%). Average maximal diameter on pathological evaluation was 3.2 +/- 1.3 cm (range 1.5 to 6). Nonenhanced computerized tomography was available in 7 of 11 cases, of which 3 of 7 (42%) showed hyperdense lesions and 4 of 7 (57%) showed isodense lesions. The percent of fat identified per high power field was less than 25% in 12 of 13 fat poor angiomyolipoma lesions (92%) compared to 2 of 4 classic lesions (50%) known to be angiomyolipoma before surgery ($p = 0.04$).

Conclusions: We suggest that a general definition of fat poor angiomyolipoma should be the failure of imaging to reveal fat within a lesion, thus, making it unsuspected at surgery. A pathological definition should be less than 25% fat per high power field, which to our knowledge is a formerly undefined quantity. Not all cases are hyperdense on nonenhanced computerized tomography. These lesions cannot be reliably identified by imaging and they should be managed like all enhancing renal masses.

Editorial Comment

CT is the method of choice for identification of angiomyolipomas (AMLs), even those with small amounts of fat. However, 5-14% of these tumors do not present detectable fat by CT examination. Classically the finding of a homogeneously hyperdense renal mass on pre-contrast scans with homogeneously and prolonged enhancement on contrast-enhanced scans, has been considered suspicious for AML without radiological evidence of fat.

The authors present an original contribution to this subject by showing that fat poor AMLs tended to have less than 25% fat per high power field when compared with AMLs with radiological evidence of fat. We agree with the authors regarding the unreliable criteria for specific imaging diagnosis of AMLs without radiological evidence of fat. When there is no detectable fat within a single or multiple renal mass by CT, two main differential diagnoses should be considered: renal cell carcinoma and oncocytoma. Thus, CT or US-guided percutaneous biopsy of the renal mass should be performed in order to establish the correct diagnosis before surgery.

Dr. Adilson Prando

*Chief, Department of Radiology
Vera Cruz Hospital
Campinas, São Paulo, Brazil*

Combined MRI and MR Spectroscopy of the Prostate before Radical Prostatectomy

Wetter A, Engl TA, Nadjmabadi D, Fliessbach K, Lehnert T, Gurung J, Beecken WD, Vogl TJ

Institute for Diagnostic and Interventional Radiology, University of Frankfurt, Frankfurt, Germany
AJR Am J Roentgenol. 2006; 187: 724-30

Objective: The purpose of this study was to evaluate a routine protocol for combined MR and spectroscopic imaging of the prostate for staging accuracy.

Subjects and methods: Fifty patients with biopsy-proven prostate carcinoma were examined with our sequence protocol, which consisted of T2-weighted fast spin-echo sequences and a pelvic T1-weighted spin-echo sequence. For spectroscopy, we used a 3D chemical shift imaging (CSI) spin-echo sequence. Image interpretation was performed by two radiologists. The total number of tumor voxels and tumor voxels per slice were counted to estimate the tumor volume in every patient. The potential of MR spectroscopy to differentiate between T2 and T3 tumors, based on the estimated tumor volumes, was compared with the staging performance of MRI.

Results: The MR measurement time was 19.01 minutes, and the total procedure time averaged 35 minutes. Seventy-six percent of the spectroscopic examinations were successful. Statistically significant differences in the number of tumor voxels per slice and tumor volumes were found between T2 and T3 tumors. The descriptive parameters of MRI and MR spectroscopy did not differ significantly; sensitivity and specificity were 75% and 87%, respectively, for MRI and 88% and 70%, respectively, for MR spectroscopy. The combination of both methods resulted in only a slight improvement in staging performance and was not statistically significant. Conclusion: Combined MRI and MR spectroscopy of the prostate has no diagnostic advantage in staging performance over MRI alone. The mean tumor volumes, estimated by MR spectroscopy, differ statistically significantly between T2 and T3 tumors.

Editorial Comment

Nowadays, the ideal way to adequately stage prostate cancer is by the combination of conventional MRI techniques and 3D-MR spectroscopic imaging (MRSI). In other words, 3D-MRSI of the prostate must be done together with conventional MRI. MRSI can be useful for the diagnosis and detection of extra-prostatic disease and seminal vesicle invasion based on the capability of estimation of tumor volume and tumor location. The presence of more than 4 contiguous voxels with cancer indicates higher probability of extra-prostatic extension of the disease. The authors of this manuscript concluded that the differences of the staging performance between MRI and MRSI were not statistically significant and thus they do not recommend the routine use of their combined sequence protocol for staging purposes of patients with histologically proven prostate carcinoma. By using their spectroscopic technique, they also had relatively unexpected high rates of false positive (13%) and false negative (25%).

We must consider these data with caution since several important aspects of the technique used by the authors should be discussed since the authors used different parameters from those currently used by other investigators. First 3D-MR spectroscopic imaging is acquired by water and lipid-suppressed double-spin-echo point-resolved spectroscopy sequence, which is optimized for quantitative detection of both choline and citrate. Data sets are acquired as $16 \times 8 \times 8$ phase-encoded spectral arrays (1024 voxels; nominal spatial resolution, 0.34 cm^3 ; 1000/130; acquisition time, 17 minutes. The authors used a 3D-MRSI technique where by choosing k-space-weighted acquisition, the scanning time was shorter, 10 minutes 45 seconds, for a $12 \times 12 \times 8$ scan with a TR of 1,300 milliseconds and four averages. With the application of a Hamming filter, the voxel size was increased from a nominal $6.7 \times 6.7 \times 10 \text{ mm}$ to an effective size of $10 \times 10 \times 15 \text{ mm}$ corresponding to an effective volume of 1.5 cm^3 . The nominal voxel size obtained by the authors was 0.45 cm^3 significantly larger than 0.34 currently used. When we increase the nominal voxel size we might expect undesirable partial volume and loss of spatial resolution. This can be considered one important drawback of their technique and perhaps could explain their higher rates of false-negatives results. Another important point to discuss is that the authors did not mention whether they replaced or not the air within the endorectal coil by liquid perfluorocarbon. Liquid perfluorocarbon is very useful to reduce the high magnetic field susceptibility at the air-tissue interface and improve the quality of MR spectroscopic imaging data (by reducing the line width). Among 50 patients evaluated in this study, the authors had only 38 patients (76%), with MR spectroscopic imaging sufficient for analysis. One might speculate that by using perfluorocarbon within the endorectal coil instead of air their results would be significantly better.

Another point that we must consider is that the authors uses a higher value of the ratio choline + creatine / citrate to consider tumor voxel. They consider, tumor voxel when the ratio of (choline + creatine) / citrate was equal to or higher than 1.1. Although there is no consensus about spectral interpretation, the classification system described by Kurhanewicz et al (1) has been used in the more recent studies on this subject. In that system, voxels are considered suspicious for cancer if the ratio of choline and creatine to citrate is at least 2 standard deviations (SDs) higher than the average ratio for the normal peripheral zone. Voxels are

considered very suspicious for cancer if the ratio of choline and creatine to citrate is higher than 3 SDs above the average ratio (equal or higher than 0.86). By using a considerably higher ratio to consider tumor voxel one could expect larger number of false negative.

In our opinion, the association of conventional MRI and 3D-MRSI is very important for the outcome of a patient with prostate cancer.

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Dr. Adilson Prando
Chief, Department of Radiology
Vera Cruz Hospital
Campinas, São Paulo, Brazil

UROGENITAL TRAUMA

Predicting Major Hemorrhage in Patients with Pelvic Fracture

Blackmore CC, Cummings P, Jurkovich GJ, Linnau KF, Hoffer EK, Rivara FP

Harborview Injury Prevention and Research Center, University of Washington School of Public Health and Community Medicine, Seattle, Washington, USA

J Trauma. 2006; 61: 346-52

Background: Pelvic fractures can be an important source of major hemorrhage in victims of blunt trauma. However, no rapid and reliable noninvasive method exists for predicting which subjects will have major hemorrhage. The objective of this study is to use information available upon presentation to the trauma center to develop a clinical prediction rule to identify subjects with pelvic fracture who are at high risk of major hemorrhage.

Methods: A retrospective cohort study was performed on all subjects with pelvic fracture from blunt force mechanism at a single level one trauma center during a 4.3 year period. Chart review identified findings from initial pelvic radiographs and from emergency department care including mechanism of injury, and hemodynamic status. Major hemorrhage was defined by angiographic findings, transfusion requirement and pelvic hemorrhage volume. Logistic regression was used to formulate a clinical prediction rule to stratify subjects based on probability of major hemorrhage.

Results: Complete data were available on 627 of 783 eligible subjects. Predictors of major hemorrhage included emergency department hematocrit 30 or less, pulse rate of 130 or greater, displaced obturator ring fracture and pubic symphyseal wide diastasis. Combinations of predictors defined groups with probability of major hemorrhage from 1.6% to 66%.

Conclusions: Probability of major pelvic fracture related hemorrhage can be estimated from initial pelvic radiograph, pulse, and hematocrit.

Editorial Comment

When dealing with pelvic fractures and a hypotensive patient (in shock) it is essential to first determine where the bleeding is coming from, whether from the chest, abdomen or pelvis. Initial methods to determine this are by physical exam, plain films of the pelvis and chest, and FAST scan. When the bleeding source is the pelvis,

bleeding is either from a venous and/or arterial source. Pelvic fractures that increase the volume of the true pelvis can result in massive blood loss. Open book pelvic fractures are examples of potential great blood loss since a small increase in pelvis radius results in a volume increase of radius cubed. Methods to control venous bleeding then are to reduce the pelvic fracture and return the true pelvis to its original size. Such methods to reduce and stabilize pelvic fracture include pelvic binder, C clamp device, pelvic external fixation device, and internally rotating the lower legs and tying them together. For arterial bleeding, embolization of the pelvic vessels via angiography is typically needed.

Dr. Steven B. Brandes

*Associate Professor, Division of Urologic Surgery
Washington University in St. Louis
St. Louis, Missouri, USA*

Abdominal Computed Tomographic Scan for Patients with Gunshot Wounds to the Abdomen Selected For Nonoperative Management

Velmahos GC, Constantinou C, Tillou A, Brown CV, Salim A, Demetriades D

Department of Surgery, Division of Trauma and Critical Care, University of Southern California Keck School of Medicine, Los Angeles County/University of Southern California Medical Center, Los Angeles, California, USA

J Trauma. 2005; 59: 1155-60; discussion 1160-1

Background: Computed tomographic (CT) scanning is increasingly used in patients with abdominal gunshot wounds (AGSWs) selected for nonoperative management (NOM). Triple-contrast CT scanning (i.e., intravenous, oral, and rectal) has produced encouraging initial results. The exact role and usefulness of CT scanning with intravenous contrast only is unknown.

Methods: Hemodynamically stable AGSW patients without generalized abdominal tenderness were offered a trial of NOM, underwent single-contrast (intravenous) CT scanning, and were prospectively followed from July 1, 2002, to May 31, 2004. The sensitivity and specificity of CT scanning to detect organ injuries requiring repair were calculated against the clinical results of NOM. The effect of CT scanning in management was recorded.

Results: One hundred patients with nontangential AGSWs were included. Twenty-six required laparotomy, which was nontherapeutic in five (19%). These five patients underwent operation on the basis of misleading CT findings (n = 3) or development of clinical symptoms (n = 2). Two CT scans were false-negative, and these patients were operated on at 121 and 307 minutes after arrival for hollow visceral injuries and recovered without postoperative complications. Three CT scans were false-positive and resulted in nontherapeutic laparotomies without postoperative complications. The sensitivity and specificity of CT scanning was 90.5% and 96%, respectively. CT findings resulted in a change of management in 40 patients. In nine, the decision to operate was changed to a decision to manage nonoperatively; whereas in eight, the opposite occurred. In addition, in 17, the decision to observe was changed to a decision to discharge; whereas in 1, the opposite occurred. Finally, five patients had additional tests after the findings of CT scanning.

Conclusion: Abdominal CT scanning is a safe and useful method of selecting AGSW patients for NOM. Further exploration is needed to define the precise benefits of routine CT scanning over clinical examination with selective CT scanning.

Editorial Comment

It is well accepted that most blunt trauma to solid organs can be managed effectively by a nonoperative approach. In the past, it was dogma that all penetrating injuries to the abdomen or retroperitoneum required surgical exploration. However, there is mounting evidence that in the properly selected patient, there has been a paradigm shift to an increasing nonoperative or expectant management of penetrating abdominal injuries (where the patient has no peritoneal signs and is hemodynamically stable). Overall, kidney injuries that end up needing surgical exploration is often determined by the mechanism of injury, namely, blunt trauma 2 to 4 %, stab wounds roughly 50%, and gunshot wound roughly 75%. The reason penetrating injuries more commonly require exploration is that the injuries are typically of higher Grade 3 to 5, which more commonly require exploration. Logically, grade for grade, kidney injuries should be treated the same, regardless of the mechanism. Thus, in highly select cases where the kidney is an isolated injury, expectant management can be considered. The proviso being that delayed bleeding may be more common, and secondary procedures such as selective embolization or ureteral stent placement needed in a delayed fashion.

Dr. Steven B. Brandes

*Associate Professor, Division of Urologic Surgery
Washington University in St. Louis
St. Louis, Missouri, USA*

PATHOLOGY

A Working Group Classification of Focal Prostate Atrophy Lesions

De Marzo AM, Platz EA, Epstein JI, Ali T, Billis A, Chan TY, Cheng L, Datta M, Egevad L, Ertoy-Baydar D, Farree X, Fine SW, Iczkowski KA, Ittmann M, Knudsen BS, Loda M, Lopez-Beltran A, Magi-Galluzzi C, Mikuz G, Montironi R, Pikarsky E, Pizov G, Rubin MA, Samaratunga H, Sebo T, Sesterhenn IA, Shah RB, Signoretti S, Simko J, Thomas G, Troncoso P, Tsuzuki TT, van Leenders GJ, Yang XJ, Zhou M, Figg WD, Hoque A, Lucia MS

Johns Hopkins University School of Medicine, USA

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Focal atrophy is extremely common in prostate specimens. Although there are distinct histologic variants, the terminology is currently nonstandardized and no formal classification has been tested for interobserver reliability. This lack of standardization hampers the ability to study the biologic and clinical significance of these lesions. After informal and formal meetings by a number of the authors, focal atrophy lesions were categorized into 4 distinct subtypes as follows: (i) simple atrophy, (ii) simple atrophy with cyst formation, (iii) postatrophic hyperplasia, and (iv) partial atrophy. In phase 1 of the study, pathologists with varying levels of experience in prostate pathology were invited to view via the Internet a set of “training” images with associated descriptions of lesions considered typical of each subtype. In phase 2 of the study, each participant provided diagnoses on a series of 140 distinct “test” images that were viewed over the Internet. These test images consisted of the 4 subtypes of atrophy and images of normal epithelium, high grade prostatic intraepithelial neoplasia, and carcinoma. The diagnoses for each image from each pathologist were compared with a set of “standard” diagnoses and the kappa statistic was computed. Thirty-four pathologists completed both phases of the study. The interobserver reliability (median kappa) for classification of lesions as normal, cancer, prostatic intraepithelial neoplasia, or focal atrophy was 0.97. The median kappa for the classification of atrophy lesions into the 4

subtypes was 0.80. The median percent agreement with the standard diagnosis for the atrophy subtypes were: simple 60.6%, simple with cyst formation 100%; postatrophic hyperplasia 87.5%; partial atrophy 93.9%. The lower percentage for simple atrophy reflected a propensity to diagnose some of these as simple atrophy with cyst formation. Seven pathologists completed the phase 2 analysis a second time, and their intraobserver reproducibility was excellent. Three of 4 pathologists with low agreement with the standard diagnosis for simple atrophy improved their scores after repeating the analysis after re-examination of the “training set” of images. In conclusion, these criteria for variants of focal prostate atrophy may facilitate studies to examine the relation between various patterns of prostate atrophy and prostate cancer.

Editorial Comment

Seven pathologists with interest and expertise in genitourinary pathology took part in a sponsored meeting to present a morphological classification for prostatic atrophy: simple atrophy, postatrophic hyperplasia, simple atrophy with cyst formation and partial atrophy. Other morphological classifications for prostatic atrophy also exist (1,2). The histologic subtypes of prostatic atrophy do not represent distinct entities but a morphologic continuum of acinar atrophy (3). Subtyping atrophy is useful only to allow recognition of the lesion and to distinguish it from mimics. The study surveyed checked the inter-reproducibility among 34 pathologists from 25 different institutions from 10 different countries of the morphological classification proposed by 7 pathologists.

Prostatic atrophy is one of the most frequent benign mimickers of prostatic adenocarcinoma (4). Atrophy is commonly associated with chronic prostatitis which may have an active component characterized by presence of neutrophils. The lesion can also be the result of treatment with radiation and antiandrogens. Although many examples of atrophy are still considered idiopathic in nature, in cases of age related atrophy there is strong evidence that it may be a manifestation of chronic ischemia due to local arteriosclerosis (1).

Some reports suggest that focal atrophy may be causally linked to prostate cancer and to other pre-neoplastic lesions (5). However, other studies do not support this hypothesis (1,2). Another exciting link of atrophy is related to serum PSA levels. We have just finished in our Institution a study showing that, regardless of cause, there is a significant positive association between extent of atrophy and serum total or free PSA elevation in patients with biopsies showing no cancer, high-grade prostatic intraepithelial neoplasia (HGPIN) or areas suspicious for cancer (ASAP). The findings suggest that damaged epithelial cells in atrophic acini may be source of serum PSA elevation.

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Dr. Athanase Billis
*Full-Professor of Pathology
State University of Campinas, Unicamp
Campinas, Sao Paulo, Brazil*

Widespread High-Grade Prostatic Intraepithelial Neoplasia on Prostatic Needle Biopsy: A Significant Likelihood of Subsequently Diagnosed Adenocarcinoma

Netto GJ, Epstein JI

Department of Pathology, The Johns Hopkins Hospital, Baltimore, MD, USA

Am J Surg Pathol. 2006; 30: 1184-8

In comparison with earlier studies, recent reports have demonstrated a lower incidence of prostate carcinoma after an initial diagnosis of high-grade prostatic intraepithelial neoplasia (HGPIN). The latter has led to a general tendency to reconsider the absolute need for a rebiopsy in this setting. The current retrospective study assesses the subsequent likelihood of identifying prostatic adenocarcinoma (PCa) in 41 patients with an initial diagnosis of "widespread" HGPIN defined as HGPIN present in 4 or more biopsy cores. All patients underwent at least 1 follow-up (F/U) sampling procedure in a period of 1 to 41 months. PCa was found in 16/41 patients (39%), all except 1 identified on the first F/U biopsy with the remaining patients diagnosed on a transurethral resection after a negative first F/U biopsy. All but 1 prostatic carcinoma diagnoses were obtained within 2 years from initial biopsy with 10 rendered within the first year. On average, prostate cancer was identified at 10.4 months (range: 1 to 36). One-fourth of all identified prostatic carcinomas were of Gleason score 7 or more. In 4 additional patients (9.7%), F/U biopsy revealed HGPIN with adjacent atypical small glands suspicious but not diagnostic of carcinoma (PINATYP). Of 41 patients, 10 (24.3%) continued to show HGPIN with the remaining 11/41 patients (26.8%) showing benign prostatic tissue. Patients ≥ 70 years of age at the time of initial biopsy had a statistically significant higher rate of PCa or HGPIN/PINATYP diagnosis on repeat biopsy compared with younger patients ($P=0.02$), with 55% of older men being diagnosed with cancer as compared with 33% in younger men. Patients with fewer cores sampled on initial biopsy were more likely to be diagnosed with carcinoma as opposed to HGPIN/PINATYP on F/U ($P=0.015$). Other factors such as the number of F/U procedures, serum prostate-specific antigen level before initial HGPIN biopsy, number of cores per F/U biopsy, and F/U interval length did not affect the likelihood of finding carcinoma. In summary, our study reveals a 39% risk of finding PCa on repeat biopsies obtained after an initial diagnosis of widespread HGPIN. Our findings support the need for a repeat biopsy in this subset of patients.

Editorial Comment

There are many evidences for the association of high-grade prostatic intraepithelial neoplasia (HGPIN) and prostatic carcinoma (1): the cytologic features are similar, both are located most frequently in the peripheral zone, both have more than 3 times the proliferative activity of benign glands, highest grade of PIN has loss of basal cell layer that is similar to carcinoma, increased frequency, extent and severity of PIN in the presence of carcinoma, age incidence peak precedes carcinoma, and similar immunophenotype.

Atypical glandular proliferation, dysplastic lesion, atypical lesion, intraductal dysplasia among others were designations used to refer to this lesion. In 1989 (2), in a workshop sponsored by the American Cancer Society in Bethesda, a unified nomenclature was adopted: prostatic intraepithelial neoplasia (PIN). Considering that grade 1 (low-grade) PIN has a very poor reproducibility among pathologists and a very low (if any) association to carcinoma, it is proposed to report only grade 2 or 3 PIN (high-grade PIN)

Recent reports have shown that due to an increased needle biopsy core sampling, which detects many associated cancers on initial biopsy, there is a decreased incidence of cancer following a diagnosis of HGPIN. Due to this facts, it is now recommended that men do not need routine repeat needle biopsy within the first year following the diagnosis of HGPIN (3). The study surveyed showed that there is an exception to this recommendation in case HGPIN is extensive (present in 4 or more cores). In this case there is a 39% risk of finding prostate cancer on repeat biopsies.

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Dr. Athanase Billis
Full-Professor of Pathology
State University of Campinas, Unicamp
Campinas, Sao Paulo, Brazil

INVESTIGATIVE UROLOGY

Concentration of Elastic System Fibers in the Corpus Cavernosum, Corpus Spongiosum, and Tunica Albuginea in the Rabbit Penis

Maia RS, Babinski MA, Figueiredo MA, Chagas MA, Costa WS, Sampaio FJ
Urogenital Research Unit, State University of Rio de Janeiro, Rio de Janeiro, RJ, Brazil
Int J Impot Res. 2006; 18: 121-5

The corpus cavernosum (CC) extracellular matrix is essential for normal penile erection and is implicated in erectile dysfunction. Although investigations of these issues have used the rabbit CC, organization of its components is not well known to date. We characterized and quantified the volumetric density (Vv) of the elastic system fibers in the corpus spongiosum (CS), CC and tunica albuginea (TA) of the rabbit penis. Adult New Zealand rabbits (n = 10) were used. The penile mid-shaft fragments were fixed with 4% phosphate-buffered formalin solution and/or Bouin's liquid for 24-48 h, and processed using standard histological techniques. The sections were stained with Weigert's Fucsin-Resorcin with previous oxidation. The elastic system fibers Vv (%) was determined in 25 random fields of each fragment, using the M-42 test grid. The histochemical methods detected elastic system fibers in CS, CC and TA of all animals. The Vv of elastic fibers average was 25.03+/-2.0% for CC, 32.23+/-1.41% for CS and 22.38+/-3.61% for TA. Results for CC and CS were not significantly different. The great amount of elastic fibers distribution beneath the endothelium suggests that these fibers may have an important role in the erection process in rabbits. The present data should therefore provide important information for devising experiments and interpreting results when using the rabbit penis as a model for penile dysfunctions, especially when making comparisons with humans.

Editorial Comment

The general understanding of the morphological changes and physiology of penile erection has been obtained considering different animal models such as rats, domestic animals, primates and rabbits. Therefore, normative data on the erectile tissue of these animals are important when studying diverse physiological situations and experimental pathological conditions, and comparing the findings obtained with findings in humans.

The purpose of this study was to better understanding the rabbit penis using morphometrical analysis of the elastic fibers in the corpus spongiosum (CS), corpus cavernosum (CC) and tunica albuginea (TA).

A previous study demonstrated that the volumetric density (Vv) of elastic system fibers in the rat CC was 9%, and therefore, it was concluded that the cellular and matricial components of the rat CC differ markedly from those of humans in content and organization (1). Consequently, inferences and correlations based on physiological

and pathological findings derived from experiments that use the rat as an erection model may be misleading if these differences are not considered.

In mammals, the classification of different penis types is based on erectile or connective tissue. In animals with vascular penis (rabbit or man), erection is a consequence of increase in size and hardening of the organ. In animals with a fibroelastic penis, the erection is essentially a result of length increasing, with the penis emerging from the prepuce due to sigmoid flexure straightening (2).

Interesting, the present study showed that the elastic system fibers were abundant in the CS of the rabbit, demonstrating a greater Vv in contrast to the CC and TA. It was demonstrated that the New Zealand rabbit penis is a vascular organ with prominent elastic fibers in the CS (Vv = 32.3%) and CC (Vv = 25.1%), as well as in the TA (Vv = 22.4%). It was observed a larger amount of elastic fibers in the rabbit penis than in human penis components. As the rabbit has been used as the better animal model for studying erectile function, this information is of utmost importance and should be taken into account when comparing the experimental findings with those of humans.

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Dr. Francisco Sampaio

*Full-Professor and Chair, Urogenital Research Unit
State University of Rio de Janeiro
Rio de Janeiro, Brazil*

Expression of COX-2 in Normal and Pyelonephritic Kidney, Renal Intraepithelial Neoplasia, and Renal Cell Carcinoma

Mungan MU, Gurel D, Canda AE, Tuna B, Yorukoglu K, Kirkali Z
Dokuz Eylul University School of Medicine, Department of Urology, Izmir, Turkey
Eur Urol. 2006; 50: 92-7; discussion 97

Objectives: The role of inflammation in carcinogenesis is unknown. To determine the relationship between cyclooxygenase 2 (COX-2) expression, inflammation, and carcinogenesis in human renal cell carcinoma (RCC), we looked for COX-2 expression in normal and pyelonephritic kidney, renal intratubular neoplasia (RIN), and RCC tissues.

Methods: COX-2 expression was assessed immunohistochemically in tissues obtained from 20 pyelonephritic kidneys, 16 normal kidneys, 19 RIN, and 75 RCC cases.

Results: COX-2 expression was found to be positive in 64% of RCCs. It was positive in 13 chronic pyelonephritic (65%), 9 normal (56%), and 15 RIN (79%) cases. COX-2 expression was significantly higher in RCC and RIN than the normal and pyelonephritic cases ($p < 0.001$ and $p < 0.001$, respectively). No statistically significant difference was noted between RCC and RIN cases.

Conclusions: Although the function of COX-2 in tumor development has not been exactly elucidated, the increased expression of COX-2 in RIN and RCC might be a factor that may play a role in the development of RIN or progression to RCC, which warrants further research.

Editorial Comment

Results of previous studies support the importance of neovascularity in tumor growth and that cyclooxygenase 2 expression may be an important regulator of neovascularity in renal cell carcinoma. The authors of this study found that there is no significant difference between cyclooxygenase 2 expression in normal and pyelonephritic kidney tissues. It is indicative of differences in the mechanism of inflammation in pyelonephritis (infectious agents) and peritumoral inflammation occurring around the tumor due to anti-tumor immune response, which could induce cyclooxygenase 2 expression. The authors pointed out that the peritumoral kidney tissue inflammation seems to have different molecular characteristics than inflamed kidney tissue in pyelonephritis, such as increased cyclooxygenase 2 expression. Although preclinical and in the experimental setting, this paper opens new avenue in the treatment of renal cell carcinoma, that is the use of cyclooxygenase 2 inhibitors.

Dr. Francisco Sampaio

*Full-Professor and Chair, Urogenital Research Unit
State University of Rio de Janeiro
Rio de Janeiro, Brazil*

RECONSTRUCTIVE UROLOGY

Botulinum Toxin Injections for Neurogenic and Idiopathic Detrusor Overactivity: A Critical Analysis of Results

Patel AK, Patterson JM, Chapple CR

Sheffield Teaching Hospitals NHS Trust, Urology Research Department, Royal Hallamshire Hospital, Sheffield, United Kingdom

Eur Urol. 2006; 50: 684-709; discussion 709-10

Objective: In recent years there has been an increasing use of the botulinum neurotoxins for the management of conditions characterised by detrusor overactivity. Early studies showed promising results in an area where few options previously existed between pharmacotherapy and surgery. This has led to an urgent need to assess the wide range of techniques and therapies available, as well as the efficacy and tolerability of the treatment. We performed a critical analysis of the numerous clinical studies for this novel treatment option in the management of neurogenic and idiopathic detrusor overactivity, with a view to directing further research and assisting urologists in the management of these conditions.

Methods: A systematic review of the literature, as well as a search for abstracts presented to relevant peer-reviewed meetings, was performed. All articles from 1988 onwards were included, prior to which no articles describing urologic use of botulinum neurotoxins had been published, although the majority of the articles have been published since 2000.

Results and Conclusions: Although many of the studies were small, overwhelming evidence supports the efficacy, safety, and tolerability of the botulinum toxins, specifically serotype A, for the management of these conditions. Before this is accepted as a widespread treatment modality, good-quality evidence from large-scale randomised controlled trials is needed. These studies should identify not only the most appropriate patients to treat but also the best dose, administration technique, and frequency for treatment.

Editorial Comment

The use of botulinum toxin in the treatment of both idiopathic detrusor overactivity (IDO) and neurogenic detrusor overactivity (NDO) is well-established clinical practice. However, as it is not an approved treatment option its use still is off label.

Schurch et al. were the first to describe the potential of botulinum toxin in the field of urology (1). In their pioneering work they were able to show botulinum toxin to be an effective, minimally invasive approach in the treatment of detrusor sphincter dyssynergy.

Two recent papers by Schulte-Baukloh et al. and by Patel et al. respectively provide the most comprehensive overview of the state of the art of the field.

Schulte-Baukloh also includes a critical assessment of Capsaicin and Resiniferatoxin (RTX) as possible alternatives to botulinum toxin. However, both drugs will probably play no more than minor roles in future long-term treatments, especially due to their limited availability as released drugs.

Patel gives the most complete overview to date of all published studies on the different types of botulinum toxin.

Both papers assess, summarize and highlight the treatment effectiveness of botulinum toxin over the past 18 years. However, emphasis must again be drawn to the fact that botulinum toxin is still unlicensed and therefore off label in the field of urology.

All studies on botulinum toxin to date have found overwhelming evidence of its efficacy, safety and tolerability. Even more, its use has demonstrably led to significant improvements in the patients' quality of life - an aspect often overlooked or forgotten. On top of that, it should be noted that NOB major surgeries, in particular, can be avoided or at least be delayed through use of botulinum toxin.

Despite of all this positive evidence a lack of worldwide, multi-center, double blind, placebo-controlled clinical trials inhibits the use of botulinum toxin from being more generally accepted. Only 3 placebo-controlled studies (2 on NDO, 1 on IDO) are mentioned by Patel attesting to the urgent need of carrying out accordingly designed studies.

Consequently, several such trials have been initiated or are under way right now. Until they will have been completed the drug should primarily be used at designated centers to increase our understanding of its properties and applications.

Comparison of the different types of botulinum toxin is difficult because of variations in their individual molecular structures and mechanisms of action. The precise mechanism underlying the effects on smooth muscle cells and the nervous system is still not fully understood - as opposed to the well-studied effect guiding the onset of action in the striated muscle - opening further fields of study.

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K.D. Sievert, B. Winter, A. Stenzl
Department of Urology
Eberhard-Karls-University Tuebingen
Tuebingen, Germany

Neuromodulatory Therapies in Female Pelvic Medicine and Reconstructive Surgery: Biological Agents

Schulte-Baukloh H, Knispel HH

Department of Urology, St. Hedwig Hospital, Teaching Hospital of University Hospital Charite, Berlin, Germany

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In recent years, important improvements in the management of patients with neurogenic or non-neurogenic detrusor overactivity and urge incontinence have been brought about by the introduction of vanilloids and botulinum toxins in urology. In this review we introduce the new therapeutic options, provide basic information, and summarize the results experienced so far.

Neobladder Emptying Failure in Males: Incidence, Etiology and Therapeutic Options

Simon J, Bartsch G Jr, Kufer R, Gschwend JE, Volkmer BG, Hautmann RE

Department of Urology, University of Ulm, Ulm, Germany

J Urol. 2006; 176: 1468-72; discussion 1472

Purpose: Neobladder reconstruction is considered the best option for patients requiring cystectomy. Limited information is available about incidence, etiology and therapeutic options for neobladder emptying failure in males.

Materials and methods: In a retrospective study we analyzed the data of a consecutive series of 655 male patients (age range 23 to 82 years, median 63; followup range 0 to 208 months, median 36.5) who received an ileal neobladder following radical cystectomy at our institution. All patients had a complete followup until death or until December 2003. Data on all diagnostic and therapeutic procedures performed for neobladder emptying failure were collected.

Results: Of 655 patients 75 (11.5%) had at least 1 episode of failure emptying the neobladder requiring some form of therapy during followup. Failure was due to dysfunctional voiding in 23 patients (3.5%) and mechanical obstruction in 52 patients (8%). Causes of mechanical obstruction were benign strictures of the neovesicourethral anastomosis (23 patients, 3.5%) or the anterior urethra (11 patients, 1.7%), neoplastic obstruction by local tumor recurrence (13 patients, 2.0%) or a nonurological malignancy (1 patient, 0.2%), and obstruction by mucosal valves (3 patients, 0.5%) or a foreign body (1 patient, 0.2%). In 38 of 52 patients with mechanical obstruction of the neobladder outlet emptying was fully restored with endourological procedures, while in 14 of 52 patients long-term catheterization was necessary. Catheterization was the therapy of choice for all patients with dysfunctional voiding.

Conclusions: Neobladder emptying failure is of major concern but is not an argument against orthotopic diversion. The overall rate of transient or permanent neobladder emptying failure in males is high but most of the mechanical causes can be managed endoscopically, while the rate of patients with long-term catheterization for dysfunctional voiding is relatively low.

Editorial Comment

The authors report on the emptying problems in their vast experience in male patients with an orthotopic neobladder. 75 of 655 patients (11, 5%) had problems with emptying of the neobladder requiring therapy after follow up of up to 208 months. The biggest group of patients were those with a stricture of the neovesicourethral anastomosis (3, 5%) followed by a local tumour recurrence (2, 0%) and urethral strictures (1, 7%). In the recent literature with six major retrospective publications who analyzed this issue, a rate of outlet obstruction, mainly

as anastomotic strictures was found in 4.5 – 17.5% within 6 – 8 months after the surgery. Compared to these data, the authors have only 3.5% of anastomotic strictures, which is at the lower end.

The good message about the report of these problems is that the majority of patients did regain volitional voiding, generally after one endoscopic treatment (with the exception of pelvic tumour recurrences). This led to the conclusion by the authors that despite a fairly large emptying failure in this series most of these problems were of mechanical origin and could thus be managed endoscopically.

It is of note, too, that apparently none of the anastomotic tumor recurrences was treated either surgically or by radiotherapy. One can speculate that the anastomotic tumour recurrences were a consequence of a more cranial pelvic recurrence. It may, however, also have been possible that due to the omission of endoscopy during the follow up a recurrence was only diagnosed at a time when surgery was not a possibility anymore.

From this large series one can also see that a neobladder valve obstructing the outlet can be found in male patients as well. We have seen and published obstructing ileal valves as a possible reason of urinary retention in female patients. Obstructing ileal valves seem to be a possibility in male patients as well and are leading to the same therapeutic consequence, i.e. transurethral valve resection (1). The similar observation in male patients was seen with dysfunctional voiding: It was present in 2% of male patients and almost always led to long term catheterization.

Altogether a nice series of a not so rare problem in both male and female neobladder patients. For those performing such a procedure and those dealing with these patients during follow up it is definitely a recommendable manuscript.

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Dr. Arnulf Stenzl & Dr. Karl-Dietrich Sievert

*Department of Urology
Eberhard-Karls-University Tuebingen
Tuebingen, Germany*

UROLOGICAL ONCOLOGY

Cystectomy for Transitional Cell Carcinoma of the Bladder: Results of a Surgery Only Series in the Neobladder Era

Hautmann RE, Gschwend JE, de Petriconi RC, Kron M, Volkmer BG
Department of Urology, Faculty of Medicine, University of Ulm, Germany
J Urol. 2006; 176: 486-92; discussion 491-2

Purpose: We studied the effect of radical cystectomy for transitional cell carcinoma of the bladder on survival and failure patterns when the 2 surgical standards cystectomy and neobladder were combined, when possible. **Materials and methods:** A consecutive series of patients undergoing radical cystectomy with pelvic lymph node dissection for transitional cell carcinoma of the bladder with curative intent was analyzed. Patients with neoadjuvant radiotherapy/chemotherapy were excluded. Pathological characteristics based on the 2002 TNM system, recurrence-free/overall survival and metastatic patterns were determined.

Results: A total of 788 patients with a mean age +/- SD of 65 +/- 10 years and a mean followup of 53.5 months who underwent surgery between 1986 and 2003 were analyzed. A neobladder was constructed in 75.4% of patients. Ten-year recurrence-free and overall survival rates were 59.1% and 44.9%, respectively. Positive lymph nodes were present in 143 patients (18%). The rate of recurrence-free survival at 5 years was 82.5% for pT2a pN0, 61.9% for pT2b and pT3a pN0, and 53.1% for pT3b pN0 disease. Local and distant failure rates were 4% and 9.5% for organ confined tumors, 15.9% and 19.2% for nonorgan confined tumors, and 20.4% and 45.1% in patients with positive lymph nodes, respectively.

Conclusions: In patients with organ confined, lymph node negative transitional cell carcinoma excellent survival data can be achieved as long as the tumor is limited to the inner half of the detrusor. These data on a large group of patients support early aggressive surgical management for invasive bladder cancer. The results of this surgery only series may serve as a reference for other treatment modalities for bladder cancer.

Editorial Comment

This impressive series of cystectomy only in all stages of transitional carcinoma is certainly a reference for other treatment modalities – as the authors themselves proudly state.

Still some aspects may be worth considering. An overall tumor-specific survival rate of roughly 60% after 10 years means that 40% of patients have died of their tumor. These 40% certainly deserve more or other therapy than cystectomy only as their disease was not cured finally. Looking more closely into the N+ group with roughly 15% recurrence-free survival after already 5 years, or into the T3bN0 group with 42 % recurrence-free survival after 10 years may support this statement. Adjuvant systemic chemotherapy, still far from ideal, might be one of such therapies to consider in these high-risk patients, as recent metaanalyses suggest.

Dr. Andreas Bohle

Professor of Urology

HELIOS Agnes Karll Hospital

Bad Schwartau, Germany

Safety and Efficacy of Intravesical Bacillus Calmette-Guerin Instillations in Steroid Treated and Immunocompromised Patients

Yossepowitch O, Eggener SE, Bochner BH, Donat SM, Herr HW, Dalbagni G

Department of Urology, Memorial Sloan-Kettering Cancer Center, New York, New York, USA

J Urol. 2006; 176: 482-5

Purpose: We assessed the safety and efficacy of intravesical bacillus Calmette-Guerin instillations in steroid treated and immunocompromised patients.

Materials and methods: We retrospectively reviewed the charts of 697 patients treated with bacillus Calmette-Guerin instillations at our institution from 1991 to 2004. In 24 patients (3.5%) an underlying comorbidity directly affecting the immune system was diagnosed before bacillus Calmette-Guerin administration or steroids were administered at least 6 weeks before and at the time of bacillus Calmette-Guerin instillations. The immunosuppressive effect of steroids was assessed by the percent of lymphocytes. End points were the bacillus Calmette-Guerin response at 6 months, defined as normal cystoscopy, cytology and biopsy when available, and treatment related toxicity.

Results: Four patients (17%) had active lymphoma or chronic lymphocytic leukemia during bacillus Calmette-Guerin administration and 21 (88%) had a concurrent condition for which oral steroids (11), inhaled steroids

(14) or oral and inhaled steroids (4) were administered. Patients treated with oral steroids had a lower percent of lymphocytes than patients treated with inhaled steroids and 15 age matched patients with high risk superficial bladder cancer and no steroid treatment (12.3% vs 17.5% and 18.6%, respectively). The overall bacillus Calmette-Guerin response rate at 6 months was 58%. Ten of the 24 patients had disease recurrence and 3 had disease progression at a median followup of 63.5 months (IQR 19.5, 89). One patient treated with oral steroids had self-limited febrile disease and worsening of myalgia 48 hours after his third bacillus Calmette-Guerin cycle. No other systemic adverse event following bacillus Calmette-Guerin therapy was recorded and all patients completed scheduled treatments.

Conclusions: Intravesical bacillus Calmette-Guerin is a viable therapeutic option in patients with high risk superficial bladder cancer and concomitant lymphoma or chronic lymphocytic leukemia, treatment with low dose oral steroids or treatment with inhaled steroids. The bacillus Calmette-Guerin response rate at 6 months and the side effects profile associated with bacillus Calmette-Guerin therapy in these patients were comparable to those in patients with no evidence of immunosuppression. Further studies are warranted to assess the safety and efficacy of bacillus Calmette-Guerin instillations in critically immunocompromised patients.

Editorial Comment

Intravesical BCG is the most effective immunotherapy to date. An effective immune system is deemed necessary on one hand to transfer the local immune response against live mycobacteria into efficacy against urothelial cancer and on the other hand to restrict the more or less inevitable mycobacterial colonization of the bladder and even systemic bacteremia. So what happens if the immune system is compromised?

This paper gives an important answer to this question. According to their data, no complications occurred in immunocompromised patients and even more important, no major side effects were seen.

This experience is supported by own and others personal experience in such patients. Still, from own published experiments in mice a more effective immune ablation by steroids might result in complete ineffectiveness of BCG and the risk of systemic spread, so the good results reported here might just reflect relative low immunosuppressive dose of corticosteroids.

In conclusion after careful risk and benefit evaluation BCG might be given in individual immunocompromised cases.

*Dr. Andreas Bohle
Professor of Urology
HELIOS Agnes Karll Hospital
Bad Schwartau, Germany*

NEUROUROLOGY & FEMALE UROLOGY

The Effect of Terazosin on Functional Bladder Outlet Obstruction in Women: A Pilot Study

Kessler TM, Studer UE, Burkhard FC

Department of Urology, University of Bern, Bern, Switzerland

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Purpose: We assessed the effect of terazosin (Hytrin®) on functional bladder outlet obstruction in women.

Materials and methods: Functional bladder outlet obstruction was defined as a maximum flow rate of less than 12 ml per second combined with a detrusor pressure at maximum flow rate of more than 20 cm H₂O in pressure

flow studies in the absence of neurological disorders or mechanical causes. In a prospective pilot study 15 women with functional bladder outlet obstruction were treated with terazosin. Terazosin was initiated at 1 mg daily and gradually increased to the maintenance dose of 5 mg daily during 2 weeks. Symptoms and urodynamic parameters were assessed before and 3 to 4 weeks after the initiation of alpha-blocker therapy.

Results: While on terazosin, voiding symptoms subjectively improved greater than 50% in 10 of the 15 women ($p = 0.002$). Median maximum urethral closure pressure at rest decreased significantly from 98 to 70 cm H₂O ($p = 0.001$), median maximum detrusor pressure decreased from 45 to 35 cm H₂O ($p = 0.008$), median detrusor pressure at maximum flow decreased from 34 to 27 ml per second and median post-void residual urine decreased from 120 to 40 ml ($p = 0.006$ and 0.002 , respectively). There was a significant increase in the median maximum flow rate from 9 to 20 ml per second and in median voided volume from 300 to 340 ml ($p = 0.0005$ and 0.021 , respectively). Storage symptoms, functional urethral length and maximum cystometric capacity did not change significantly with alpha-blocker therapy ($p > 0.05$). Overall terazosin resulted in a significant improvement in symptoms and urodynamic parameters in 10 of the 15 women (67%).

Conclusions: Terazosin had a significant symptomatic and urodynamic effect in two-thirds of our patients. These results suggest that terazosin may be an effective treatment option in women with voiding dysfunction due to functional bladder outlet obstruction.

Editorial Comment

The authors review the efficacy of terazosin on functional bladder outlet obstruction in women. In this prospective study 15 women diagnosed with functional bladder outlet obstruction (as opposed to mechanical outlet obstruction) were treated with terazosin beginning at a dose of 1 mg with gradual increase to a maximum dose of 5 mg over a two week period. Patient's symptoms and urodynamic studies were assessed at the onset of the study and approximately one month after the initiation of the terazosin therapy. The authors found that two-thirds of the women had improvement in their voiding symptoms as well as an improvement in the urodynamic studies examined. Simply stated, the investigators found that terazosin had both a subjective and objective improvement in two-thirds of the study patients.

With this paper, the authors delve into the complex world of non-neurogenic female voiding dysfunction. The difficulty of diagnosis and the relative lack of understanding of this malady has been discussed in the literature (1). That only two-thirds of the patients experienced symptomatic improvement may be secondary to the potential cause of voiding dysfunction being secondary to the failure of relaxation of the striated urethral sphincter(2). The discussion section of this paper is excellent and provides a great deal of information upon which many may expand their understanding of functional bladder outlet obstruction in women.

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Dr. Steven P. Petrou

*Associate Professor of Urology
Chief of Surgery, St. Luke's Hospital*

*Associate Dean, Mayo School of Graduate Medical Education
Jacksonville, Florida, USA*

Prevalence and Occurrence of Stress Urinary Incontinence in Elite Women Athletes

Caylet N, Fabbro-Peray P, Mares P, Dauzat M, Prat-Pradal D, Corcos J

Laboratory of Functional Exploration of the Nervous System, Nimes University Hospital Centre, Nimes, France

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Objective: 1) To assess the prevalence of stress urinary incontinence (SUI) and urge urinary incontinence (UTI) in elite women athletes versus the general female population, and 2) to analyze the conditions of occurrence of urine loss in search of etiological clues in elite athletes.

Decision: An anonymous self-questionnaire was collected transversally from women aged 18 to 35 years. The exposed group was composed of elite female athletes; the non-exposed group was made up of women in the same age range accepting to answer the questionnaire.

Results: A total of 157 answers from elite athletes and 426 from control subjects were available for analysis. Urinary incontinence prevalence was 28% for athletes and 9.8% for control subjects ($p = .001$). There was no significant difference in the relative prevalence of SUI between the athletes and control subjects. Athletes reported urine loss more frequently during the second part of the training session ($p < 0.0003$), and the second part of competition ($p < 0.05$). Urinary incontinence prevalence was 9.87% in physically-active control subjects versus 9.84% in sedentary control subjects (NS). Even a small quantity of urine loss was felt to be embarrassing. Most incontinent women did not dare to speak of their condition to anybody.

Conclusions: There is a very high prevalence of urinary incontinence in women athletes. Detailed studies of the patho-physiology of this problem are necessary to formulate preventive recommendations.

Editorial Comment

As stated by the authors, this was an epidemiologic study of the presence of urinary incontinence in female athletes and a controls. The two groups were not age matched but fairly close. The authors found a statistically significant difference between athletes and physically active women with regards to the prevalence of urinary incontinence. Parity was not found to be a risk factor in the elite athlete study group. Of note, though both groups complained of incontinence, < 5% of either group wore any incontinence protection such as pads or shields. It seemed, as noted in the figures of the paper, that swimmers had one of the highest rates of urinary incontinence thus giving support to those who value highly chlorinated swimming pools. In addition, there are few among the readership who would challenge the athletes participating in the fight category to their claim of 0% of urinary incontinence. It would have been of interest for the authors to have included the incontinence rates in the subgroup of elite athletes participating in gymnastics and weightlifting: the internet has provided ample pictures of ill-timed episodes of urinary loss during weightlifting competitions. It was interesting to see that when looking at the group of women who participated in physical exercise but were not classified as nationally competitive athletes, that physical activity did not seem to be a risk factor for incontinence. It will be of keen interest to examine the rate of response to pelvic floor exercise and therapy in the group of elite level national athletes; will this highly disciplined and physically trained group have a higher success rate than the general population of patients which are seen in our usual practice.

Dr. Steven P. Petrou

Associate Professor of Urology

Chief of Surgery, St. Luke's Hospital

Associate Dean, Mayo School of Graduate Medical Education

Jacksonville, Florida, USA

PEDIATRIC UROLOGY

Augmentation Cystoplasty Rates at Children's Hospitals in the United States: A Pediatric Health Information System Database Study

Lendvay TS, Cowan CA, Mitchell MM, Joyner BD, Grady RW

Children's Hospital and Regional Medical Center, University of Washington School of Medicine, Seattle, WA, USA

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Purpose: We identified augmentation cystoplasty rates in children with spina bifida at children's hospitals enrolled in the Pediatric Health Information System database.

Materials and Methods: The Pediatric Health Information System database tabulates demographic and diagnostic patient data from 35 children's hospital centers in the United States. Between October 1999 and September 2004 we extracted data on 0 to 19-year-old patients with International Classification of Diseases-9 diagnosis codes for spina bifida. The International Classification of Diseases-9 procedure code for augmentation cystoplasty was cross-referenced with these patients to determine the total number of patients with augmentation, total population augmentation rates and individual institution rates of bladder augmentation.

Results: Staff at enrolled pediatric medical centers submitted inpatient data accounting for 9,059 beds servicing an aggregate metropolitan population of 82 million individuals. In the 5-year period 12,925 unique spina bifida patient encounters were identified, including 665 patients who underwent augmentation cystoplasty. The mean 5-year institutional number of augmentations performed in children with spina bifida was 20 (range 1 to 121) and the mean annual number of augmentations performed per institution was 4. The overall augmentation rate at 33 hospitals contributing data for the full years 2000 to 2003 was 5.4% (range 0.5% to 16.3%, $p < 0.0001$). The male-to-female ratio of those who underwent augmentation was 1:1.2. Median length of stay in children with augmentation was 7 days (mean 9). The median age of children with augmentation was 10.4 years, that is 11.3 years in boys and 9.8 years in girls. The difference in mean age was statistically significant ($p < 0.003$). At institutions where 10 or more augmentations were performed in 5 years (mean 27) mean patient age at operation was 10.1 years. This was significantly younger than the mean patient age of 12.3 years at hospitals where fewer than 10 augmentations (mean 5) were done in 5 years ($p < 0.05$).

Conclusions: Clinical management for neurogenic bladder conditions has evolved to emphasize nonoperative management. Several studies suggest that aggressive early intervention improves bladder compliance and may protect renal function. However, results from the Pediatric Health Information System database demonstrate no change in augmentation rates during this time and they demonstrate significant interinstitutional variability. To our knowledge this represents the largest series of augmentation cystoplasty in children with spina bifida to date.

Editorial Comment

The authors review the PHIS database, which is a data set that includes 33 children's hospitals, about 70% of all free standing children's hospitals in the United States. They looked specifically at all children admitted to a hospital in their database with the diagnosis for spina bifida, between 10/1999 and 9/2004. There were 12,925 admissions for the diagnosis of spina bifida and of these, 534 were for augmentation cystoplasty. They examined information about this procedure in particular. Some findings were pretty standard. The length of stay was around 7 days and the mean age of the patients undergoing augmentation was 11.3 for boys and 9.8 for girls. Interestingly, the rate of augmentation remained stable throughout the study period, but there were marked variations between hospitals. Also of note, the rate of augmentation in an individual hospital had little to do with the overall number of hospitalizations for spina bifida in that hospital.

These large data sets have the advantage of looking at actual practice patterns and allow for comparisons of different institutions. In these respects, studies like this are extremely useful. The finding of no change in the rate of augmentation over time is a bit disappointing in that the advent of aggressive neonatal medical management has been thought to reduce the need for augmentation. Moreover, as the life-long risks of augmentation become increasingly clear, one would guess that ever more caution would be exercised in the use of the procedure. Interestingly, this was not seen.

Also striking is the enormous variation between hospitals. One hospital did approximately 105 augmentations (of about 600 admissions) whereas during the same time period another did only about 7 (of about 550 admissions). Both are clearly high volume centers with significant interest in the care of these patients, yet with extreme variability in their urological management.

One major weakness of the data set is the lack of outcome information. What a terrific opportunity exists to look at patient reported outcomes in these two centers! Unfortunately, in this data set, the centers are de-identified. Maybe in the future someone will take this on. Until then, we await more information from striking studies like this.

Dr. Barry A. Kogan

*Chief and Professor of Urology and Pediatrics
Albany Medical College
Albany, New York, USA*

Nocturnal Enuresis in Adolescents and Adults Is Associated With Childhood Elimination Symptoms

Bower WF, Sit FK, Yeung CK

Division of Paediatric Surgery and Paediatric Urology, Department of Surgery, Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, New Territories, Hong Kong

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Purpose: Since nocturnal enuresis in adults and adolescents is rarely monosymptomatic, we identified the prevalence of childhood bladder and bowel dysfunction, and compared findings to those in a normative cohort. **Materials and Methods:** Childhood and current bladder and bowel dysfunction were investigated in 56 consecutive adolescents and adults attending a public nocturnal enuresis service and in 293 normative adults using a self-administered questionnaire. Analysis involved descriptive statistics, the chi-square and Kruskal-Wallis tests, and regression analysis with $p < 0.05$ considered significant.

Results: Adolescents and adults attending a public nocturnal enuresis service had significantly higher childhood scores than normative adults, and significantly more childhood urgency, frequency, urge incontinence, infrequent voiding and small volume, high urge voids. Infrequent bowel action and fecal soiling in childhood were also significantly more common in those with nocturnal enuresis than in controls. Adult symptoms of urge incontinence, general bowel symptoms and nocturnal enuresis were significantly more common in adults and adolescents with nocturnal enuresis. Significant associations were found between childhood symptoms and adult overactive bladder, and childhood emptying dysfunction and adult voiding dysfunction. Higher childhood scores in adults and adolescents with nocturnal enuresis correlated significantly with current adult symptoms of urge, urge leakage, stress incontinence, hesitancy, incomplete emptying and UTI within the last year.

Conclusions: Significant childhood bladder and bowel symptoms along with more adult urge and bowel dysfunction were found in adults and adolescents with nocturnal enuresis. The association with adult urgency and urinary tract infection supports the likelihood of underlying bladder and or voiding dysfunction in unremitting nocturnal enuresis.

Editorial Comment

The authors report the results of two prospective questionnaire surveys, comparing adolescents and adults with nocturnal enuresis to those with a non-urological (ENT) problem. They find that older patients with nocturnal enuresis frequently have urge incontinence (45% vs. 8%) and may have bowel symptoms (16.4% vs. 12.6%). In addition, the adult patients with enuresis had markedly higher recollection of childhood problems like urgency, frequency and urge incontinence, as well as constipation and fecal soiling.

This study is another in a growing literature suggesting that adults with voiding problems, often have a history of childhood voiding and bowel problems. Although we do not know the number of children who outgrow their childhood issues and never recur as adults, it is clear that a large number of adults with problems had childhood symptoms. This emphasizes the critical need for new innovative and effective treatment modalities for children with voiding problems.

Also interesting is the finding that adults with continued nocturnal enuresis have a large likelihood of reporting symptoms of overactive bladder, despite often being labeled “monosymptomatic nocturnal enuresis.” This has several implications. First, it suggests that clinicians should look harder for an urge component in children with this condition. It is probably underlying in many, but may not be symptomatic as children can control their voids and fluid intake during the day. Second, it suggests a mechanism by which the clinician can approach adults with this condition. Both anticholinergic and alpha-adrenergic blockers can reduce overactive bladder symptoms and should be considered as adjuncts in behavioral management.

Dr. Barry A. Kogan
Chief and Professor of Urology and Pediatrics
Albany Medical College
Albany, New York, USA