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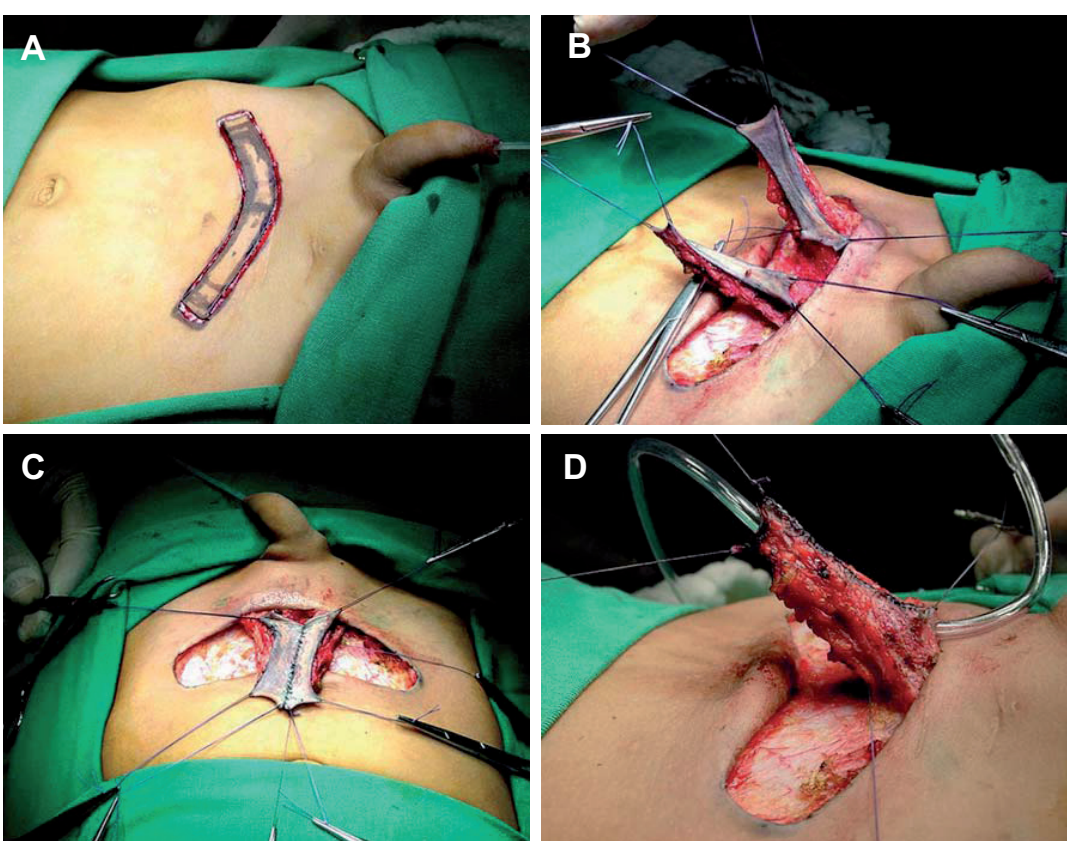

Channel alternative to the Mitrofanoff principle: construction of a tube with two skin flaps (Page 205)

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EDITOR'S COMMENT

Lower Pole Nephrolithiasis

The March – April 2009 issue of the International Braz J Urol presents important contributions from different countries, and as usual, the editor's comment highlights some papers.

Doctor Arzoz-Fabregas and co-workers, from Instituto Universitario Dexeus, Barcelona, Spain, evaluated on page 140 the efficacy of extracorporeal shock wave lithotripsy (SWL) on lower calyceal calculi in relation to the renal anatomical factors and determine which of these factors can be used to select patients who will benefit from SWL. The authors analyzed retrospectively 78 patients with single radiopaque lower calyceal stones treated with SWL. The patients were evaluated 3 months after lithotripsy with a simple abdominal X-ray and a kidney ultrasound scan. In the follow-up, 39 patients were stone-free, while 39 patients had residual fragments. The authors concluded that lower Infundibular height could be a good measurement tool for deciding which patients with lower calyceal lithiasis would benefit from SWL treatment. Height of less than 22 mm suggests a good outcome from lithotripsy. Dr. Bannakij Lojanapiwat, from Chiangmai University, Thailand, Dr. Udo Nagele, from Tubingen University, Germany and Dr. Ricardo Miyaoka, Dr. W. K. Durfee & Dr. Manoj Monga, from University of Minnesota, USA, well-known experts in lower pole nephrolithiasis, provided important editorial comments on this paper.

Doctor Westphalen and colleagues, from Department of Radiology, University of California San Francisco, USA, retrospectively determine on page 171 the accuracy of T2-weighted endorectal MR imaging in the detection of prostate cancer after external beam radiation therapy and to investigate the relationship between imaging accuracy and time since therapy. The study included 59 patients who underwent 1.5 Tesla endorectal MR imaging of the prostate between 1999 and 2006 after definitive external beam radiation therapy for biopsy-proven prostate cancer. Two readers recorded the presence or absence of tumor on T2-weighted images. It was found that 34 of 59 patients (58%) had recurrent prostate cancer detected on biopsy. The overall accuracy of T2-weighted MR imaging in the detection cancer after external beam radiation therapy was 63% (37/59) for reader 1 and 71% for reader 2 (42/59). For both readers, logistic regression showed no difference in accuracy between those imaged within 3 years of therapy and those imaged more than 3 years after therapy. The authors concluded that T2-weighted endorectal MR imaging has low accuracy in the detection of prostate cancer after external beam radiation therapy, irrespective of the time since therapy. Dr. Adilson Prando, from Vera Cruz Hospital, Campinas, São Paulo, Brazil, and Dr. Ronaldo Baroni, from University of São Paulo, Brazil, provided important and balanced editorial comments on this paper.

Doctor Kim and collaborators, from Chonnam National University Medical School, Gwangju, Korea, assessed on page 183 the factors associated with osteoporosis in Korean men with non-metastatic prostate cancer before undergoing androgen deprivation therapy (ADT). The patients were divided into 2

groups: group I, non-metastatic prostate cancer (n = 42) and group II, benign prostatic hypertrophy (BPH; n = 130). The lumbar bone mineral density (BMD) was evaluated using quantitative computed tomography. The demographic, health status, lifestyle, body mass index (BMI), serum testosterone concentration, and disease variables in prostate cancer (Gleason score, clinical stage, and PSA) were analyzed prospectively to determine their effect on the BMD. The authors found that the risk factors for osteoporosis in men with prostate cancer include a low BMI, and elevated serum PSA. They proposed that monitoring BMD from the outset of ADT would be a logical first step in the clinical strategy to avoid or minimize potential bone-related complications in these patients. Dr. A. M. Brufsky, from University of Pittsburgh School of Medicine, USA, commented the paper.

Doctor Macedo and co-authors, from Federal University of Sao Paulo, Unifesp, Sao Paulo, SP, Brazil, reported on page 205 the technical feasibility of a new approach for creating catheterizable channels in a rabbit model and presented a preliminary clinical experience. The authors configured a tube from 2 rectangular skin flaps 1x4 cm opposite each other in the middle line of the lower inferior abdomen. The channel was anastomosed to the bladder dome with embedding sutures to create a valvular mechanism. The technique proved feasible in all animals, 9 of 12 could be easily catheterized and underwent urodynamic study. No stoma leakage was observed in 7 animals at high bladder pressures (> 50 cm H20) and only 2 animals had some leakage at 40 cm H20. The mean follow-up of the clinical series (3 patients) was 7.2 months. Two patients remained continent up to 4 hours, whereas 1 patient had some leakage after 2 hours. The authors were able to confirm feasibility of a new extra-abdominal channel based on the Mitrofanoff principle and successfully reproduced the method in a clinical setting. Dr. Lorenzo, from Hospital for Sick Children, Toronto, Canada, provided a very important balanced editorial comment on this paper.

Doctor Domingos and co-investigators, from Ribeirao Preto Medical School, USP, SP, Brazil, investigated on page 217 the histological features and biocompatibility of a latex biomembrane for bladder augmentation using a rabbit model. After a partial cystectomy, a patch of a non-vulcanized latex biomembrane (2x4 cm) was sewn to the bladder with 5/0 monofilament polydioxanone sulfate in a watertight manner. Groups of 5 animals were sacrificed at 15, 45 and 90 days after surgery and the bladder was removed. No death, urinary leakage or graft extrusion occurred in any group. All bladders showed a spherical shape. Macroscopically, after 90 days, the latex biomembrane was not identifiable and the patch was indistinguishable from normal bladder. A bladder stone was found in one animal. The authors concluded that the latex biomembrane is biocompatible and can be used in models for bladder augmentation in rabbits. It promotes epithelium and muscle regeneration without urinary leakage. Dr. Tomasz Drewa, from Nicolaus Copernicus University, Bydgoszcz, Poland, and Dr. Stacy T. Tanaka, from Monroe Carell Jr. Children's Hospital at Vanderbilt, Nashville, Tennessee, USA, provided interesting comments on this paper.

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

Review Article
International Braz J Urol Vol. 35 (2): 125-139, March - April, 2009

Laparoscopic Radical Prostatectomy: A Review

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ABSTRACT

Introduction: We offer an overview of the intra-, peri- and postoperative outcomes of laparoscopic radical prostatectomy (LRP) with the endpoint to evaluate potential advantages of this approach.
Materials and Methods: We conducted an extensive Medline literature search (search terms "laparoscopic radical prostatectomy" and "radical prostatectomy") from 1990 until 2007. Only full-length English language articles identified during this search were considered for this analysis. A preference was given to the articles with large series with more than 100 patients. All pertinent articles concerning localized prostate cancer were reviewed.
Conclusion: Pure LRP has shown to be feasible and reproducible but it is difficult to learn. Potential advantages over open surgery have to be confirmed by longer-term follow-up and adequately designed clinical studies.

Key words: *prostate neoplasms; prostatectomy; laparoscopy; urinary incontinence; erectile dysfunction; training*
Int Braz J Urol. 2009; 35: 125-39

INTRODUCTION

Open radical retropubic prostatectomy (RRP) is widely considered the treatment of choice for localized prostate cancer (1). After the first feasibility report by Schuessler (2) in 1997 and the standardization of the laparoscopic radical prostatectomy (LRP) technique by Guillonneau et al. (3) in 1999, a progressively growing interest has risen in the urologic community for LRP. Since then, the advantages and pitfalls of this minimally invasive approach have been increasingly reported in the literature by different authors (4). The lower blood loss and transfusion rate associated with the laparoscopic approach together with shorter hospital stay, reduced catheterization time, better pain control and the faster return to everyday activities seem the most encouraging improvements obtained (5). However, the interpretation of the data presented in the literature continues to be debated and has yet to be clarified.

This review reports intra-, peri- and post-operative outcomes of LRP with the endpoint to evaluate potential advantages of this approach.

Historical Aspects

In 1992 Schuessler, a non-academic, attempted the first LRP assisted by two endourologists with laparoscopic experience in renal surgery (6). These pioneers were able to successfully perform 9 LRP procedures, but found no benefit over open prostatectomy (2).

In 1997 Gaston, who had an extensive experience in laparoscopic pelvic floor reconstruction, started LRP (7) but only one year later Guillonneau et al. detailed their stepwise approach to transperitoneal LRP (3). These experiences were followed shortly

by several European centers (8-11). In USA, even experienced laparoscopists remained very skeptical about LRP. Gill and Zippe, who at that time focused on renal laparoscopic surgery, were one of the few who established a program of laparoscopic pelvic surgery (12).

LRP has slowly risen in popularity. In 2002, a survey of laparoscopic activities in Germany and Switzerland revealed that 15% of the departments performed LRP, but only 5% did more than 15 cases (13). In 2004, 19.2% of German departments already offered LRP, whereas 26.9% preferred perineal, and 60.6% retropubic radical prostatectomy (14). In 2006, a multi-center study of more than 5800 patients was published treated with LRP by 50 surgeons in Germany (15).

MATERIALS AND METHODS

We conducted an extensive Medline literature search (search terms "laparoscopic radical prostatectomy" and "radical prostatectomy") from 1990 until 2007; only full-length English language articles identified during this search were considered for this analysis. A preference was given to the articles with larger series of more than 100 patients. The laparoscopic results were interpreted as whole regardless of the technical differences (transperitoneal versus extraperitoneal, antegrade versus retrograde dissection, number, disposition of the surgical ports, etc).

We have to underline that since 1997 the number of publications regarding the laparoscopic radical prostatectomy has greatly increased. A research in the Pubmed literature from 1990 until 1997, with the terms "laparoscopic radical prostatectomy" and "laparoscopic prostatectomy", produced less than 10 results; the majority of the articles publicized during this period concerned the laparoscopic pelvic lymphadenectomy in conjunction with radical perineal or retropubic prostatectomy in patients with prostate cancer. In the middle of the 90s the interest regarding laparoscopic pelvic lymphadenectomy (including urologic laparoscopy in general) diminished; the new methods for staging prostatic cancer that progressively appeared (based on the combination of Gleason score with PSA value) eliminated the indication of pelvic lymphadenectomy in more than 95% of the cases of prostate cancer potentially treated by surgical intervention.

After 1997 LRP became, in some centers, the surgical approach of choice for the treatment of the localized prostate cancer.

INTRA- AND PERIOPERATIVE COMPLICATIONS

The low conversion rates in all major series are a testimony to the careful introduction of LRP (16).With increasing experience, even challenging situations, such as cases following previous laparoscopic hernioplasty can be managed (17). In a recent multicenter study, technical reasons (i.e. adhesions, difficulties with the urethro-vesical anastomosis, malfunctioning of instruments) or uncertain tumor anatomy (i.e. risk of positive margins) caused the conversion to open surgery rather than intraoperative complications, such as bleeding or visceral injury (15). Bhayani et al. observed only 1.9% incidence of open conversions in a multi-institutional series citing prior pelvic surgery and morbid obesity as contributing factors (18). All of the comparative studies between LRP and RRP demonstrated a lower blood loss (LRP: 189-1100 mL vs. RRP: 550-1550 mL) and transfusion rate with laparoscopy except one (19), where the higher transfusion rate observed in the LRP series is probably correlated to the different level of surgeon expertise (RRP > 800, LRP > 60 cases). The same applies to complication and reoperation rates (7,19-26).

A comparison of the identical number of patients (n = 1243) treated at two centers in Germany demonstrates similar patterns. A comprehensive description of incidence and types of complications following 567 consecutive LRPs over a 3-year period revealed a total, major, and minor complication rate of 17%, 4%, and 14.6% respectively (27). Gonzalgo et al. applied a grading scheme designed to detail the frequency and severity of complications following LRP. A total of 34 (13.8%) morbidities were encountered during 246 LRP cases, the majority (94.1%) of which was self-limited (i.e. grade II-III). There were only 2 (5.9%) grade IV complications (i.e. potentially life

Table 1 – *Update classification of surgical complications.*

Grade	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions. Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgesics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade III	Requiring surgical, endoscopic or radiological intervention.
Grade IIIa	Intervention not under general anesthesia.
Grade IIIb	Intervention under general anesthesia.
Grade IV	Life-threatening complication (Including CNS complications)* requiring IC/ICU management.
Grade IVa	Single organ dysfunction (Including dialysis).
Grade IVb	Multiorgan dysfunction.
Grade V	Death of a patient.
Suffix "d"	If the patient suffers from a complication at the time of discharge (see examples in Table-2), the suffix "d" (for "disability") is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

**Brain hemorrhage, ischemic stroke, subarrachnoidal bleeding, but excluding transient ischemic attacks. CNS = central nervous system; IC = intermediate care; ICU = intensive care unit. Source = Dindo D, Demartines N, Clavien PA = Classification of surgical complications = a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004; 240: 205-13.*

threatening requiring intensive care unit management) and no grade V-complication (i.e. death) (28). The classification of the complication degrees mentioned above was based on the updated Clavien system that is reported in Table-1. Application of the updated Clavien grading scheme (Table-1) in the report of Guilloneau et al. (27) also resulted in approximately 90% of LRP complications classified as grade II or III. The remaining 10% of complications could be classified as grade 1 and there were no grade IV or V complications (Table-2). At centers of expertise, conversion and reintervention have become a rare event (less than 1%).

From a large number of other studies (10,27,29-31) we could deduce that there is a 4% (1-6.1%) of intraoperative complications (rectal injury 1.5% (1-2.4%), ileal or sigmoid injury 1% (0.8-1.9%), epigastric vessels injury 0.27% (0-0.5%), bladder injury 0.81% (0-1.6%), ureteral injury 0.36% (0-0.7%), external iliac vein injury 0.09% (0-0.8%). The early postoperative complications amounted to 20.7% of cases and they mainly included anastomotic

Table 2 – *Examples of the application of the update classification with regard to the complications of 2 laparoscopic radical prostatectomy series.*

	Grade I	Grade II-III	Grade IV	Grade V
Gonzalgo et al. (28)	0%	94.1%	5.9%	0%
Guillonneau et al. (27)	10%	90%	0%	0%

leakage (10.3%), hemorrhagic complications (2.8%), urinary retentions (2.35%) and ileus (1.4%). However, anastomotic stricture, phlebitis/embolism/thrombosis, urinary tract infections, neurological complications, fistulas, lymphorrea, trocar hernia accounted for percentages below 1%. Two more recent series confirm these data (15,32) (Tables-3 to 6).

The necessity of transfusion varied from 1.6% to 31% among the analyzed series (15, 29-32), Table-7.

A particular area of concern is pulmonary embolism (PE) that is the main cause of death in the 0.5% patients who die perioperatively after cancer surgery (33). The true incidence of symptomatic venous thromboembolism (VTE) in patients undergoing LRP is still unclear. Recently, Secin et al. published a multi-institutional study of VTE and PE in prostate cancer patients undergoing LRP (with or without robotic assistance). Of 5951 patients retrospectively evaluated, 31 developed symptomatic VTE (0.5%;

Table 3 – *Intraoperative morbidity of laparoscopic radical prostatectomy in early series with more than 100 patients.*

	Hoznek et al. (29)	**Turk** et al. (10)	**Rassweiler** et al. (30)	**Guillonneau** et al. (27)	**Eden** et al. (31)	**Total** (%)
Number of patients	134	125	180	567	100	
Rectal injury	1.4%	2.4%	1.6%	1.4%	1%	1.5
Ileal or sigmoid injury	-	0.8%	-	1.9%	-	1
Epigastric vessels injury	-	-	-	0.5%	-	0.27
Bladder injury	-	-	-	1.6%	-	0.81
Ureteral injury	-	-	-	0.7%	-	0.36
External iliac vein injury	-	0.8%	-	-	-	0.09
Total	1.4%	4%	1.6%	6.1%	1%	4.03

Table 4 – *Early postoperative complications in early series with more than 100 patients.*

	Hoznek et al. (29)	**Turk** et al. (10)	**Rassweiler** et al. (30)	**Guillonneau** et al. (27)	**Eden** et al. (31)	**Total** (%)
	134	125	180	567	100	
Anastomotic leakage	2.9%	13.6%	19.4%	10%	1%	10.3
Hemorrhagic complications	-	1.6%	10%	1.7%	1%	2.8
Urinary retention	-	-	-	4.5%	-	2.35
Ileus	-	3.2%	2.7%	1%	1%	1.4
Anastomotic stricture	-	1.6%	3.3%	-	-	0.7
Phlebitis/thrombosis/embolism	0.7%	2.4%	-	0.3%	-	0.6
Neurological complications	0.7%	-	-	0.5%	1%	0.45
Urinary tract infections	-	-	-	-	-	0
Fistulas	0.7%	0.8%	1.1%	-	-	0.36
Lymphorrea	2.9%	-	-	0.1%	-	0.45
Trocar hernia	-	-	0.5%	-	1%	0.18
Other	2.2%	0.8%	0.5%	1.4%	-	1.17
Total	10.4%	24%	37.7%	19.9%	5%	20.7

Table 5 *– Main intra and postoperative complications of laparoscopic radical prostatectomy in late series (Lein et al., ref. 32).*

Intra and Postoperative Complications	%
Rectal injury	3.3
Ileus/sub-ileus	2.5
Blood transfusion	2.2
Neurologic lesion	1.8
Bowel injury	0.9
Thrombosis/embolism	0.8
Bladder injury	0.4
Renal failure	0.3
Ureteral injury	0.1
Other	0.6
Total complication rate	12.9

Table 6 *– Laparoscopic radical prostatectomy in late series (German Laparoscopic Working Group, ref. 15).*

Complications	%
Bleeding	2.2
Rectal lesion	1.7
Extravasation	2.4
Thromboembolism	0.6
Total complication rate	8.9

95% confidence interval [CI], 0.4%, 0.7%). Among patients with an event, 22 (71%) had deep venous thrombosis (DVT) alone, 4 had PE without identified DVT, and 5 had both. Two patients died of PE. Prior DVT (odds ratio [OR] = 13.5; 95% CI, 1.4, 61.3), current tobacco smoking (OR = 2.8; 95% CI, 1.0, 7.3), larger prostate volume (OR = 1.18; 95% CI, 1.09, 1.28), patient re-exploration (OR = 20.6; 95% CI, 6.6, 54.0), longer operative time (OR = 1.05; 95% CI, 1.02, 1.09), and longer hospital stay (OR = 1.05; 95% CI, 1.01, 1.09) were associated with VTE in univariate analysis. Neoadjuvant therapy, body mass index, surgical experience, surgical approach, pathologic stage, perioperative transfusion, and heparin administration were not significant predictors. The authors concluded that the incidence of symptomatic VTE after LRP is low and that these data do not support the administration of prophylactic heparin to all patients undergoing LRP, especially those without risk factors for VTE (34).

SURGICAL MARGINS AND CANCER CONTROL

In the most representative series of laparoscopic radical prostatectomy follow-up is not long enough to give a definitive oncologic evaluation of its surgical efficacy. Nevertheless, preliminary data reported in these papers suggest that this approach can guarantee the same results in terms of cancer control as those of open procedures (35-38).

No cases of trocar track metastasis or local relapse have so far been reported after LRP although these complications have been reported after extensive nephrectomy and nephroureterectomy (39). The extraperitoneal approach avoids this potential risk of intraperitoneal dissemination of tumor cells (38).

Depending on the surgical approach the location of surgical positive margins differs: the apex with the RRP, the bladder neck with the Perineal radical prostatectomy, the posterolateral regions of the prostate (that contain the neurovascular bundles and prostatic pedicles) in the LRP (probably because of the instrument axis and its smaller amplitude during dissection of the prostatic pedicles, which are closer to the trocar ports) (40-42).

As concerns oncologic results of RP, these are evaluated based on the rate of positive surgical margins (that reflect the quality of tumor excision) and survival with no biological progression.

Table 7 *– Transfusion rate.*

Series	Transfusion Rate %
Hoznek et al. (29)	2.9
Turk et al. (10)	1.6
Rassweiler et al. (30)	3.1
Guillonneau et al. (27)	4
Eden et al. (31)	3
Lein et al. (32)	2.2
Rassweiler et al. (15)	4.1

The positive surgical margins (defined as the presence of cancer at the inked margin of resection on the prostatectomy specimen, (40)) influence the prognosis, as they determine a higher risk of biochemical, local and systemic progression (43).

The results on the positive surgical margin rate are summarized in Table-8. We have to consider that major series reported in literature, include the first patients operated when the LRP was in early development and the surgeons were either developing the technique or learning its application. More recent data, suggest a significant decrease of positive surgical margins over time without any evidence of downward stage migration, in both organ-confined and non-organ-confined disease (37,44-46).

Given the fact that LRP has only been regularly performed since 1998, information about long term follow-up is unavailable. Although the data continue to mature for LRP series, the short-term biochemical-free recurrence results appear similar to those reported in open radical prostatectomy experience with a biochemical recurrence-free probability between 83 and 94.5% at 3 years (37,44-47) (Table-9).

Long-term results on biochemical recurrence-free survival are eagerly awaited.

CONTINENCE

The wide range of incontinence rates reported in the literature indicates the difficulty to obtain an accurate assessment of urinary control after radical prostatectomy. Moreover, the lack of a uniform definition of post-operative continence is crucial to this problem. While some studies use a strict definition of continence as a "no pads" condition, others allow the use of 1 precautionary pad per day as determined by patient report.

LRP seems initially to offer an earlier continence recovery, but the number of continent patients at one year follow up is comparable to that after ORP. In

Table 8 *– Cancer control: positive surgical margin rate.*

	pT2	pT3	Overall Positive Surgical Margin Rate
Guillonneau et al. (1000 pts) (ref. 37)	15.5%	31%	19.2%
Rassweiler et al. (500 pts) (ref. 44)	7.4%	31.8%	19%
Stolzenburg et al. (700 pts) (ref. 45)	10.8%	31.2%	19.8%
Touijer et al. (500 pts) (ref. 46)	8.2%	17.2%	11%

Table 9 *– Progression free.*

	3-year Biochemical Recurrence-Free Probability	5-year Biochemical Recurrence-Free Probability	Definition of Progression
Montsouris (37)	90.5%		PSA > 0.1 ng/mL confirmed by a second increase
Heilbronn (44)	83%	73.1%	2 PSA values > 0.2 ng/mL
Johns Hopkins (47)	94.5%		2 PSA values > 0.2 ng/mL

incontinent patients, even the severity of incontinence seems to be similar after the two procedures (48).

The Montsouris group reported on a series of 255 patients with 12-months follow-up after LRP that 209 patients (82.3%) were pad free, 31 (12%) needed one pad a day, and 15 patients (5.9%) had urinary incontinence requiring more than two pads a day (49). Stolzenburg et al., using the same validated questionnaire, reported the results on 700 extraperitoneal LRPs. Among 500 patients who had 6 months follow-up, 419 patients (83.8%) were pad free, 52(10.4%) needed one to two pads a day, and 29 patients(5.8%) had urinary incontinence requiring more than two pads a day (45) (Table-10). Rassweiler et al. reported an experience of 450 LRPs; among the 300 men with 12-months follow-up, the continence rate was 91%. However, the authors did not state the definition of continence or the methodology of measurement used in their analysis (50). Galli et al. reported that the incidence of long-term continence following laparoscopic prostatectomy is 91.7%, which appears to be equal to that reported by major centers using either open or laparoscopic access (51).

Recently Rocco et al. demonstrated that a posterior reconstruction of the rhabdosphincter allowed a rapid recovery of the continence after transperitoneal videolaparoscopic radical prostatectomy.

They report that the musculo-fascial plate, comprised of the striated sphincter, Denonvilliers' fascia, and the dorsal aspect of the prostate, acts as a suspensory system for the prostato-membranous urethra and that its division during RP results in the loss of the posterior cranial insertion of the sphincter, the caudal displacement of the sphincteric complex, and a prolapse of the perineum. Therefore, they propose to reconstruct this musculo-fascial plate by joining the posterior median raphe with the connected dorsal wall of the RS to the residuum of the Denonvilliers fascia and to suspend it to the posterior wall of the bladder, 1-2 cm cranially and dorsally to the new bladder neck (52).

Therefore, a two-arm prospective comparative trial was carried out with 31 patients recruited for each arm. Group A underwent standard VLRP and group B underwent VLRP with RS reconstruction (VLRP-R). Continence was defined as no pads or one diaper/24 h and was assessed 3, 30, and 90 d after the procedure. At catheter removal, 74.2% versus 25% ($p = 0.0004$) of patients were continent with the VLRP-R technique versus VLRP, respectively. A statistically significant difference was present at 30 d (83.8% vs. 32.3%; $p = 0.0001$). At 90 d the difference, although still present, was not statistically significant (92.3% vs. 76.9%; $p = 0.25$) (52).

Nguyen et al. confirmed the earlier recovery of continence after posterior musculo-fascial plate reconstruction during robotic and laparoscopic prostatectomy. The authors evaluated the mean length of the membranous urethra on transrectal ultrasound(TRUS) measured before and after RP and, also, before the musculo-fascial suture that resulted 15.6, 12 and 14 mm, respectively. They concluded that reconstruction restored the length of the transected membranous urethra by a mean of 2 mm (53).

POTENCY

Comparison of data is not easy because most series of LRP include potency data only on a small subset of patients, some group report only the rate of spontaneous erection and, additionally, potency depends on preoperative sexual function, patient age, degree of neurovascular bundle preservation and fol-

Table 10 – *Continence between 2 series using the same validated questionnaire.*

	Pad Free	1-2 Pads/Day	> 2 Pads/Day
Montsouris group (12 months follow-up) (ref. 49)	82.3%	12%	5.9%
Stolzenburg et al. (6 months follow-up) (ref. 45)	83.8%	10.4%	5.8%

low-up, since potency can return months or years after surgery (54).

Laparoscopic nerve sparing prostatectomy is performed by dissecting the pedicles in an antegrade fashion. This maneuver releases the neurovascular bundle laterally and allows the dissection of the prostate. The delicate neurovascular bundle (NVB) is intimately related to the postero-lateral surface of the prostate. As such, complete avoidance of any thermal or electrical energy during lateral pedicle transection and NVB release comprises a hallmark principle during open surgery. Recently, Ong et al. provided evidence in the survival canine model that the use of hemostatic energy sources (monopolar cautery, bipolar cautery, ultrasound scissors) during NVB release was associated with significantly decreased erectile response to cavernous nerve stimulation (55). However, the use of conventional dissection with hemostatic suture ligatures did not compromise the erectile response to nerve stimulation. Current laparoscopic and robotic techniques for lateral pedicle transection fall short in this important regard, typically using either monopolar or bipolar electrocautery, or ultrasound energy with the harmonic scalpel, with or without clips.

Once postoperative potency is established patients reported ability to achieve sexual intercourse with or without the use of PDE-inhibitors. Potency rates after bilateral nerve sparing LRP have been reported from 33% to 67% in various series worldwide. Most experts agree that at least 18 months of follow-up is necessary to assess potency outcomes adequately (54).

Of their initial 550 patients, Guillonneau et al. reported in a subset of 47 consecutive patients less than 70 years of age, preoperatively potent with bilateral nerve sparing, 31 patients (66%) able to have intercourse with or without sildenafil (49). Rassweiller et al. reported that, in a subset of 41 patients preoperatively potent with bilateral nerve sparing (BNS), a 67% was able to have intercourse after the surgical procedure (50). Curto et al. referred that, in a subset of 137 patients that underwent BNS, 58.5% could have intercourse with or without sildenafil post-operatively (54) (Table-11).

A recent review of Mulhall et al. (56) underlines on the role of the artery-sparing radical prostatectomy. In fact, not all patients in whom the neurovascular bundles are preserved recover erectile function after radical prostatectomy. A significant proportion of these men have vascular abnormalities that can impact erectile function recovery after radical prostatectomy. The authors describe the available evidence supporting the need to spare not only the nerves, but also the arteries to improve erectile function recovery after radical prostatectomy.

LEARNING CURVE: THE IMPORTANCE OF THE MENTOR

Laparoscopic radical prostatectomy has been evaluated at several centers in the United States as a treatment option for localized prostate cancer. It is a technically difficult operation to perform with a steep learning curve. Fifty procedures seem to be necessary to decrease complications and increase functional outcomes (57).

A learning curve includes the necessity for continuous self-evaluation in terms of cancer control,

Table 11 – *Potency rates (with or without use of PDE5-I) after bilateral nerve sparing (BNS) procedure for patients preoperatively potent.*

Series	Number of BNS	% of Postoperative Potency with or without PDE5-I
Guillonneau et al. (ref. 49)	47	66%
Rassweiler et al. (ref. 50)	41	67%
Curto et al. (ref. 54)	137	58.5%

continence and potency. Many different methods can be used to acquire the technique: dry lab, animal live lab, cadaveric laparoscopic dissection or mentoring with an expert. All of these steps may not be essential, as laparoscopic radical prostatectomy is not too dissimilar to open prostatectomy.

The transfer of technology and surgical experience/aptitude is problematic. It has been clearly shown that weekend training courses and weekend laboratory sessions do not translate into clinical ability to perform these procedures. Colegrove et al. observed that participants in these courses rarely perform these procedures in clinical practice (58).

The transfer of training from open surgical experience to newly introduced laparoscopic skills does not occur, emphasizing the need for intensive training.

These common difficulties clearly highlight the importance of mentoring programs. The mentor is an expert in laparoscopic technique able to direct trainee operative maneuvers increasing his efficiency. Lack of progression is often cited as the most common reason for open conversion during a laparoscopic procedure; in this case the mentor ensures forward progression. The most difficult aspects of this procedure, such as suturing the dorsal vein complex and urethrovesical anastomosis, bladder neck dissection and dissection off of the rectum cannot be effectively learned through laboratory simulation.

Fabrizio et al. were the first to describe a mentorship program designed to expedite performance of laparoscopic radical prostatectomy. They invited a surgeon (mentor) who had performed 200 cases to instruct a fellowship trained laparoscopist (trainee). From March 2001 through September 2001 they performed 30 laparoscopic radical prostatectomies. The mentor performed the first 12 procedures with the trainee acting as assistant (group 1). The subsequent 18 procedures were performed by the trainee with the mentor acting as assistant (group 2). A final set of 20 procedures was performed by the trainee alone using 1 of 3 urological residents as an assistant (group 3). The transperitoneal approach was used and all suturing was intracorporeal. There was not any statistical difference in terms of median operative time between the groups 1-2 and 2-3 but only between 1-3. Mean estimated blood loss was comparable in groups 1 to 3 and not statistically different. Hospital stay was 3 days in all groups. Catheter time decreased as confidence was gained with the procedure (range 6 to 33 days). Final pathological stage was compared among the 3 groups. There was an overall increase in positive margins in groups 1 to 3 (16%, 22% and 30%, respectively, p not significant). However, the positive margin rate for stage pT2 disease was similar at 15.5% for groups 1 and 2, and 14% for group 3 (57).

Similar results were obtained in the mentor-guided experience of Skrekas et al. (59).

The authors concluded that an intensive, mentor initiated approach can decrease the learning curve and maintain outcomes.

Recently, Stolzenburg et al. suggested a modular training program for residents with no prior experience with open pelvic surgery in endoscopic extraperitoneal radical prostatectomy (EERPE). They divided the technique into 12 segments with 5 levels of difficulty. Then they designed a training program, where the resident learned the procedure in a mentor-defined schedule. During each educational EERPE, the trainee only performed the operative steps corresponding to his acquired skill level. The mentor performed the remaining parts of the EERPE, with the trainee assisting. The first 50 and consequent 100 cases performed by the residents were compared to the first 50 and last 100 cases (cases 521-621) performed by the mentor. Two residents with no prior experience with open pelvic surgery participated in the study, and required 43 and 38 procedures respectively, until they were considered to be competent. The initial 50 procedures performed completely independently by the residents had mean operative times of 176 and 173 minutes. There were 2 intraoperative rectal injuries (one patient developed recto-urethral fistula), 1 hemorrhage, and 1 lymphocele, postoperatively. The positive margin rate for pT2 disease was 14.3 and 11.5%, and for pT3 tumors 38.8 and 29.1%, respectively. After an additional 100 procedures operated by the same residents, mean operative times were 142 and 146 minutes. There was one patient who needed a transfusion. Postoperative complications requiring re-intervention were 1 hemorrhage, 2 anastomotic leakages and 4 symptomatic lymphoceles. The positive margin rate for pT2 disease was 12.8% and 6.5%, and for pT3 tumors 33.3% and 26.3% respectively.

No statistical significant differences were observed when comparing with the mentors cases.

The authors concluded that residents with no prior experience in open surgery of the pelvis can adhere to the modular training scheme and successfully perform the EERPE procedure with similar risk of complications compared to the tutor (60).

COST COMPARISON OF LRP VERSUS RRP

Despite the advantages of LRP regarding its minimally invasive character, the operative times for this procedure have been consistently longer than those of RRP (19-21) and the cost of the disposable operating room equipment is greater, suggesting that LRP is more expensive than RRP. Given the large number of men diagnosed with prostate cancer and presumably seeking treatment, it is desirable that treatment options are not only efficacious but also cost effective.

Anderson et al. analyzed the cost data from a single institution comparing LRP and RRP. They concluded that the total cost of the procedure was significantly more for LRP than for RRP (US$ 6760 vs. US$ 5253, $p < 0.001$). Most of this difference was due to surgical supply (US$ 1202 vs. US$ 145, $p < 0.001$) and operating room costs (US$ 1601 LRP vs. US$ 1141 RRP, $p < 0.001$). The room and board and pharmacy costs were significantly lower for LRP than for RRP because of the shorter mean length of stay. The laboratory/radiology and pathology costs were not significantly different (61) (Table-12).

Table 12 *– Costs comparison of laparoscopic radical prostatectomy (LRP) vs. retropubic radical prostatectomy (RRP), ref. 61.*

	LRP (US$)	RRP (US$)
Surgical supply	1202	145
Operating room costs	1601	1141
Room and board costs	496	710
Pharmacy costs	243	267
Laboratory/histology	682	667
Radiology	28	34
Transfusions	0	80
Surgeon	1668	1594
Total	6760	5253

CONCLUSIONS

After only a few years since its introduction, mid-term outcomes of LRP appear promising with regards to complications, oncologic and functional results, and have achieved equivalence to open surgery. Presently, a lower intraoperative blood loss and transfusion rates seem to be the most significant data in favor of LRP. The operating time is still somewhat longer, but many centers have already reported comparable operative times to open surgery. Further potentials of LRP are related to video-endoscopy, providing optimal visualization of the operating field. This may lead to better preservation of the structures around the urinary sphincter, improve apical dissection and preservation of the neurovascular bundle. All these potential advantages must be confirmed by longer-term follow-up and adequately designed clinical studies.

At the moment, the LRP costs are significantly greater than the costs of RRP, and this is predominantly due to the higher surgical supply and operating room costs.

New disposable instruments and acquired experience in LRP may significantly decrease the cost of the procedure.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

The authors performed a good review of one of the popular techniques in urology. They summarize main aspects of the historical evolution, complications, functional and oncological results, learning curve and cost. The historical aspects are very well presented. The authors did a very good review of the continence and potency aspects in the laparoscopic prostatectomy. Several groups, especially in the USA, discharge the patients from the hospital the next day after the retropubic operation (1), which is comparable

to laparoscopic prostatectomy. Lower blood loss and lower blood rate transfusion is the main advantage of the technique and is the only proven improvement. It is important to remember a great demand for a modular training program with a clinical proven usefulness for Urology fellows (2).

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EDITORIAL COMMENT

In an era when fewer open and pure laparoscopic radical prostatectomies (LRP) are being performed in the United States, it is important to recall the gold standard in prostate surgery and also the original minimally invasive approach. The authors provide a comprehensive review of the current literature regarding LRP. The authors fairly report on a large number of LRP series reviewing intra-operative and peri-operative outcomes, oncologic data, continence and potency outcomes. The review outlines comparisons of LRP to open RRP either head to head or as compared to historical controls and the authors conclude, rightly so, apparent equivalence in intermediate outcomes with LRP groups reporting decreased blood loss, transfusion rate and shorter hospital stay. However, other important outcomes such as margins, continence and potency measures are not as convincingly equivalent for LRP and really remain in question.

The authors articulate that 50 cases are needed to plateau on the learning curve of LRP. In fact, we believe the protracted learning curve and technical difficulty of LRP is vastly understated. In fact, the majority of US references in this article come from institutions that no longer perform LRP. Truth be told, the largest single institutional radical prostatectomy series are now being reported with use of the daVinci surgical robot and outcomes as compared to open and as compared to LRP are similar if not superior in some variables (1-4). While the experienced surgeon in laparoscopic prostatectomy may be capable of performing LRP, the wrist movements and three-dimensional vision that the robot provides certainly lends to a less physically challenging learning curve with equivalent surgical outcomes. A contemporary review of LRP should mention, as it did, the gold standard open RRP, but should also make at least reference to the latest innovation in minimally invasive prostatectomy, the daVinci robot assisted prostatectomy.

What is clearly illustrated in the present discussion is that excellent outcomes can be achieved with multiple surgical modalities. In the end, it is the surgeon's skill and not the tool used that makes the outcome. Regarding the surgical treatment for prostate cancer, there are many arrows in the quiver and it is up to the surgeon to choose what is appropriate for his/her patient.

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Can Infundibular Height Predict the Clearance of Lower Pole Calyceal Stone After Extracorporeal Shockwave Lithotripsy?

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ABSTRACT

Purpose: To evaluate the efficacy of extracorporeal shock wave lithotripsy (SWL) on lower calyceal calculi in relation to the renal anatomical factors and determine which of these factors can be used to select patients who will benefit from SWL.
Materials and Methods: We analyzed retrospectively 78 patients with single radiopaque lower calyceal stones treated with SWL. The patients were evaluated 3 months after lithotripsy with a simple abdominal X-ray and a kidney ultrasound scan. The success of the treatment, removal of all fragments, was correlated with renal anatomical factors measured in the pre-treatment intravenous urography: infundibulopelvic angle, lower infundibulum width, lower infundibulum length, ratio length/width, infundibulum height, and number of minor calyces in the lower calyceal group.
Results: Three months after SWL treatment, 39 patients were stone-free (NR group) and 39 had residual fragments (R group). Both groups presented no differences in relation to infundibulopelvic angle, width and length of the lower calyceal infundibulum, length/width ratio of the lower infundibulum or number of lower calyces. Height of the infundibulum, described as the distance between the line passing through the lowest part of the calyx containing the calculus and the highest point of the lower lip of renal pelvis, was the only parameter in which significant differences ($p = 0.002$) were found between the NR and R groups.
Conclusions: Lower Infundibular height could be a good measurement tool for deciding which patients with lower calyceal lithiasis would benefit from SWL treatment. Height of less than 22 mm suggests a good outcome from lithotripsy.

Key words: *kidney; kidney calculi; lithotripsy; anatomy; kidney calices*
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INTRODUCTION

The objective of SWL is to obtain a fragmentation of the calculus into fragments that can be expelled through the renal collecting system. However, the success of SWL also depends on the size and composition of the calculus, its location in the kidney, the anatomy of the urinary tract and some personal factors such as body mass index or patient mobility (1-4). According to Politis et al., although correct fragmentation is obtained in 98% of cases after SWL, the fragments are eliminated in only 75% (4).

Calculi in the lower calyceal group represent 24%-44% of all calculi requiring treatment (1). In this location, there are some controversial aspects as regards the efficacy of SWL, as the clearance rate is lower. It has been suggested that this phenomenon could be explained by an antigravitational position of the lower renal calyx (1,5), On the other hand, residual fragments after SWL can cause complications such as chronic pain, obstruction, sepsis and re-growth, which occasionally require an interventionist approach. For these reasons, there is an obvious need for a method which helps us to decide which treatment is the best

option for each individual patient: SWL, percutaneous surgery or flexible ureteroscopy (1,3).

Different renal anatomic factors have been described since Sampaio et al. (1) first described the anatomy of the renal collecting system using three dimensional models and correlated the measurement of the infundibulopelvic angle with the success of SWL, including infundibular width and length, the infundibular width/length ratio, infundibular height, the number of minor calyces, the volume of the renal collecting system and the pattern of dynamic urinary transport (5-15). These measurements have been studied and correlated with the success of SWL with different results.

The objective of this study was to evaluate the outcome of SWL in patients with single lithiasis of the lower renal pole and correlated it with the aforementioned anatomical factors measured during the pre-treatment intravenous urography (IVU), in order to determine which of them could be an effective predictive factor to decide whether SWL could be successful.

MATERIALS AND METHODS

We performed a retrospective analysis of 78 consecutive patients with single radiopaque lithiasis of the lower calyceal group who were treated in only one session with a Dornier Lithotripter S during a two-year period (from June 2005 to June 2007).

Patients with more than one calculus, residual fragments after prior lithotripsy, urinary tract anomalies, prior surgical maneuvers, such as a double-J catheter, or reduced mobility were excluded.

All patients were treated by the same urologist under intravenous sedation.

The results of the treatment were evaluated 3 months after lithotripsy. Stone free status was defined as the absence of any residual fragments in a simple abdominal X-ray film and kidney ultrasound scan. Depending on whether there were remaining fragments after three months, the patients were divided into two groups: group NR, (non-residual) composed of patients free from calculi and group R (residual), composed of patients with residual fragments.

Personal details as gender, age, body mass index (BMI) and affected kidney were correlated for each patient with the existence or not of residual fragments after the treatment.

The following parameters, measured on the twenty minutes IVU pre treatment film in a supine position, were correlated with the existence or not of residual fragments three months after the treatment:

Calculus Parameters

Estimated surface area of the calculus (SA)(mm2): Measured at the pre-treatment simple abdominal X-ray. Result of multiplying the length (L) and width (W) diameters of the calculus by π and by 0.25 (16). SA= L x W x π x 0.25

Number of shock waves applied: The number of shockwaves required to completely fragment the calculus was recorded in each case.

Calculus fragility index: Dividing the number of shock waves by the surface of the calculus in mm2.

Anatomical Parameters (measured at the pre-treatment IVU)

Infundibular width (mm): The narrowest point on the axis of the lower infundibulum (Figure-1).

Infundibular length (mm): Distance between the most distal point of the calyx containing the calculus and the midpoint of the lower lip of the renal pelvis (Figure-2).

Infundibular height (mm): Distance between the horizontal line passing through the lowest part of the calyx containing the calculus and the highest point of the lower lip of the renal pelvis (Figure-3).

Infundibulopelvic angle (º): The angle between the line drawn through the central axis of the lower infundibulum and the ureteropelvic axis (Figure-4).

Infundibular length/width ratio.

Number of minor calyces.

The statistical analysis was performed with the SPSS 13.0 Windows software program. We performed a descriptive analysis of all the aforementioned variables and compared them between the NR and R groups with Fisher's exact test and the

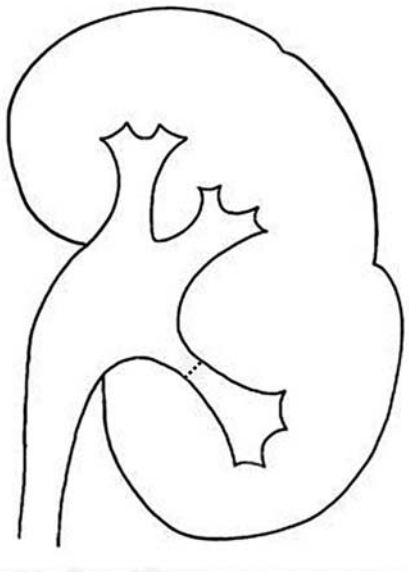

Figure 1 – *Infundibular width (mm), measured as the narrowest point in the axis of the lower infundibulum.*

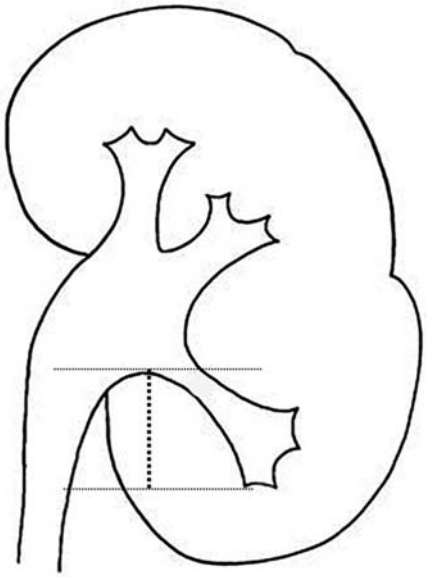

Figure 3 – *Infundibular height (mm), measured as the distance between the horizontal line passing through the lowermost part of the calyx containing the calculus and the highest point of the lower lip of the renal pelvis.*

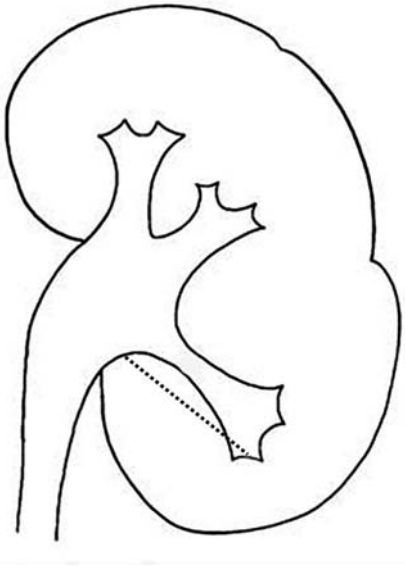

Figure 2 – *Infundibular length (mm), measured as the distance between the most distal point of the calyx containing the calculus and the midpoint of the lower lip of the renal pelvis.*

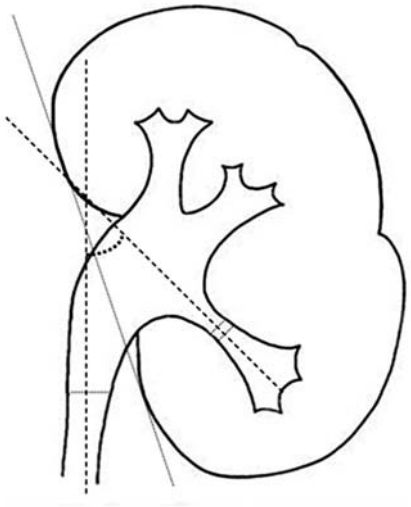

Figure 4 – *Infundibulopelvic angle (º), described as the angle between the line drawn through the central axis of the lower infundibulum and the ureteropelvic axis.*

Mann-Whitney-Wilcoxon U-test for the qualitative and quantitative variables, respectively. A logistic regression analysis was also performed to study the correlation of the existence of residual fragments with all these parameters. Finally, a ROC curve was used to choose a cut-off point for the parameters showing significant differences in the logistic regression analysis.

RESULTS

Seventy-eight patients were included in this study. Thirty-nine were classified in the NR group and the remaining thirty-nine in the R group.

Fifty per cent of the studied population was men and the other fifty per cent were women. The mean age of the patients was 48 (SD 13.4) years, and the mean BMI was 25.1 Kg/m2 (SD 4.8). Thirty-seven (47.4%) of the calculi were located in the right kidney and forty-one (52.6%) in the left. There were no significant differences regarding gender between NR and R groups (Table-1), but we found that women were more likely than men to eliminate all the fragments after SWL in our population (p = 0.023).

The median surface area of the calculi was 63 mm2 (9-450), the median number of shockwaves required to fragment them was 2000 (1000-3300) and the median number of shock waves required to fragment one surface area unit (calculus fragility index) was 31.7 waves/mm2 (111.1-7.3). Comparing the characteristics of the calculus between the two groups, there were no statistically significant differences (Table-1. Values are given as mean ± SD).

Concerning the anatomical measurements, no significant differences were found between the two groups when comparing infundibular length and width, infundibular length/width ratio, infundibulopelvic angle (IPA) or number of minor calyces. On the other hand, significant differences were found when comparing mean infundibular height in the two groups (p = 0.002), with less infundibular height found in patients who were stone-free after treatment (Table-1).

The logistic regression analysis for all the factors studied (personal, pertaining to the calculus and anatomical variables of the renal collecting system) show that only infundibular height had a significant impact on the absence of residual fragments and therefore, could be used as a predictive factor of the success of SWL in calculi located in the lower calyx (Table-2). Furthermore, the ROC curve shows that a

Table 1 – *Patients, stone and collecting system anatomical parameters. Descriptive analysis for all patients and different groups. Correlation of all the variables between group NR (non-residual fragments) and group R (residual fragments).*

Parameters	All Patients	Group NR	Group R	p Value
Sex (male: female, %)	50:50	36:64	64:36	0.023 [a]
Age (years)	48 ± 13	47 ± 14	50 ± 13	0.242
Body mass index (Kg/m2)	25.1 ± 4.7	24.9 ± 5.4	25.2 ± 4	0.515 [b]
Stone side (right: left, %)	47.4: 52.6	56.4:43.6	37.5:61.5	0.173 [a]
Stone area (mm2)	86.1 ± 70.5	84.4 ± 76.5	87.8 ± 64.8	0.745 [b]
Number of shock waves	2097.1 ± 651.8	2167.9 ± 567.2	2026.3 ± 727.4	0.473 [b]
Stone fragility (No./mm2)	35.2 ± 24.5	39.9 ± 30.5	30.4 ± 15.3	0.189 [b]
Infundibulum width (mm)	6.5 ± 8.2	6.4 ± 8.5	6.7 ± 7.9	0.781 [b]
Infundibulum length (mm)	25.9 ± 6.7	24.6 ± 4.9	27.2 ± 7.9	0.101 [b]
Infundibulum length/ width ratio	7.8 ± 6.2	6.4 ± 3.9	9.2 ± 8.6	0.380 [b]
Infundibulum height (mm)	24.1 ± 7	21.7 ± 5.6	26.6 ± 7.4	0.001 [b]
Infundibulopelvic angle (º)	51.9 ± 13.4	51.8 ± 11.6	52 ± 15.1	0.505 [b]
Number of minor calyx (%) 1 vs. > 1	43.8: 56.5	50:50	37.2:62.8	0.349 [a]

Values are given as mean ± SD, [a] for categorical parameters statistical analysis with Fisher exact test was done; [b] for quantitative variables a U-Mann-Whitney Wilcoxon sum rank test analysis was done.

Table 2 – *Logistic regression analysis.*

	B	E.T.	Wald	gl	Sig.	Exp (B)
Age	-0.003	0.027	0.013	1	0.911	0.997
BMI	0.034	0.084	0.169	1	0.681	1.035
Stone area	0.006	0.007	0.749	1	0.387	1.006
Number of waves	0.000	0.001	0.410	1	0.522	1.000
Fragility	0.036	0.025	2.044	1	0.153	1.037
I. width	-0.045	0.043	1.115	1	0.291	0.956
I. length	-0.034	0.065	0.275	1	0.600	0.967
Length / width	-0.055	0.081	0.471	1	0.493	0.946
I. height	-0.144	0.072	3.997	1	0.046	0.866
IPA	-0.018	0.024	0.554	1	0.457	0.982
Sex	-0.991	0.658	2.273	1	0.132	0.371
Constant	3.071	2.818	1.188	1	0.276	21.569

BMI = body mass index; I = infundibulum; IPA = infundibulopelvic angle.

height between 22 and 24 mm, and specifically 22.5 mm of height value could be the best cut-off point in our population for predicting response to treatment with an approximate sensitivity and specificity of 70% (Figure-5).

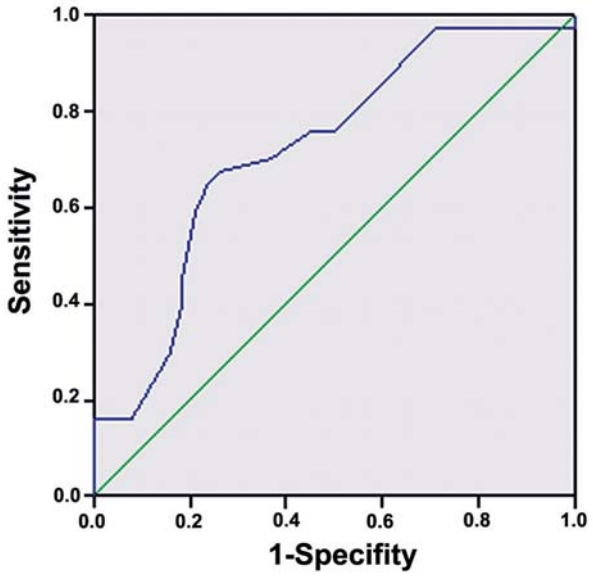

Figure 5 – *ROC curve of cut-off points for infundibular height (mm).*

ROC Curve Coordinaters

Infundibulum Height	Sensitivity	Specifity
4.00	1.000	1.000
6.00	0.973	1.000
9.00	0.973	0.974
12.50	0.973	0.947
16.00	0.973	0.895
18.50	0.973	0.737
19.50	0.973	0.711
20.50	0.757	0.500
21.50	0.757	0.447
22.50	0.703	0.368
28.60	0.676	0.268
24.50	0.649	0.237
25.50	0.495	0.211
26.50	0.595	0.184
27.50	0.405	0.184
29.00	0.297	0.158
31.00	0.162	0.079
32.50	0.162	0.000
34.00	0.135	0.000
37.50	0.081	0.000
42.00	0.054	0.000
45.00	0.027	0.000
47.00	0.000	0.000

COMMENTS

Since SWL appeared in the 1980s, most renal-ureteral calculi previously eligible for open surgery or blind endoscopic maneuvers have been successfully treated with few complications (3). However, with the development of new therapeutic techniques such as percutaneous nephrolithotomy (PCNL) or flexible ureteroscopy, the use of SWL in some situations, such as lithiasis located in the lower calyceal group, is controversial.

The objective of this study was to evaluate a population with single radiopaque lithiasis in the lower calyx, treated by SWL and fragmented into expellable particles in a single session. Depending on the response to treatment evaluated at three months with simple abdominal X-ray and kidney ultrasound scan, we divided the patients into two groups and compared them in relation to the factors which could be related to fragment expulsion, with emphasis on anatomical variables, in order to determine which of them would enable us to predict the success of SWL, thus ruling out patients who would not benefit from this treatment and who could be eligible for other therapeutic procedures such as ureteroscopy, PCNL or control of evolution (17,18).

The purpose of SWL is to disintegrate the stone into fragments of an expellable size (< 4 mm), in which success represents the complete elimination of all fragments (3). However, this often depends on factors affecting the particular patient, factors related to the calculus and factors related to the anatomy of the renal collecting system (1,3,4).

With reference to the size of lithiasis for which PCNL should be used, instead of SWL in lithiasis of the lower pole, continues to be subject to debate. Albala et al., in a multicenter prospective study analyzing lithiasis located in the lower renal pole, reached the conclusion that only calculi smaller than 1 cm are eliminated in 50% of cases after lithotripsy, and they proposed that the cut-off point for deciding between PCNL and SWL should be 1 cm (5). On the other hand, with the development of new flexible ureteroscopes, remains debated whether SWL should be the optimal choice of treatment for calculi in the lower calyceal group measuring less than 1 cm. Pearl et al., in the second phase of Lower Pole Study Group, conducted a prospective, randomized study to compare treatment by SWL and ureteroscopy of lithiasis < 1 cm in the lower pole, without finding statistically significant differences (18). In our study, we analyzed patients with lithiasis with a median surface area of 63 mm2 (9-450), equivalent to 8 mm diameter (3-21), which were fragmented into expellable fragments in a single session, as the objective was to evaluate the anatomical factors which could have an impact on fragment expulsion, instead of studying the effect of the size of the lithiasis on said expulsion. Moreover, we found no significant differences between the NR and R groups in relation to the surface area of the calculus, the number of shock waves required to fragment the stones or their fragility, measured as the number of waves divided by the surface area of the calculus.

Concerning the location of the calculus, there is some controversy concerning the efficacy of SWL, especially in lithiasis of the lower calyceal group, where a large percentage of calculi are not eliminated, regardless of their size or composition. This phenomenon is believed to be due to an antigravitational problem, which could be related to the anatomy of the calyx. The earliest studies of the anatomy of the lower calyceal group were conducted by Sampaio et al., who used polyester endocasts of cadaveric kidneys to study the length of the lower infundibulum, the width of the calyx and the IPA. According to these authors., patients with an IPA of more than 90º are more likely to eliminate the fragments after treatment with SWL (1,19). There have subsequently been more studies, such as Elbahanasy et al., who performed a retrospective analysis of the urograms examinations performed before SWL of lithiasis smaller than 15 mm in the lower calyceal group, showing that patients with a larger IPA, shorter infundibular length and greater infundibular width are those who most often eliminate the fragments after the treatment (9). Similar to Elbahanasy et al. studies we used urograms examinations before SWL in order to measure the intrarenal geometry and to find if there was any relationship with this anatomy and the stone-free status after SWL and thus classify patients into favorable or unfavorable for SWL.

Pace et al. (20) after analyzing the infundibular width on the 5, 10, 20 and compression films in supine

position, on the prone film and a film after voiding in erect position concluded that the compression film followed by the 10 and 20 minute films are the most suitable to estimate the maximum diameter of the infundibulum. In our study, we used the 20 minute film in a supine position in all the patients in order to avoid different measurements of each anatomic factor owing to the dynamic of the collecting system. To avoid the interobserver variation of different measurement described previously by Knoll et al. (2), all the parameters in our study where evaluated by the same urologist.

Despite the fact that most of the studies of the lower pole anatomy use urograms pre-treatment examinations to measure anatomic factors, it has been discussed that some of these factors like infundibular width or infundibular height should not be used because its measurement can change with different urography phases, respiration and/or postural movements or poor quality images (7,20,21). As we were more used to evaluating the collecting system by urography in the period when the study was done, we decided to perform this exploration on all the patients included in the study. Although there have been some groups that evaluated the possibility of using a three dimensional helical computed tomography to measure the anatomy of the collecting system to avoid potential bias as described above instead of using an urography some authors did not find any statistical difference which concluded that IVU remains a good method to analyze renal collecting system (20,22). IPA is the most widely measured factor when evaluating the anatomy of the collecting system and it has been measured using several methods. Sampaio et al. (1,19) calculated the angle according to the location of the lithiasis, whereas Elbahanasy et al. (9) calculated the IPA based on precise and reproducible anatomical references, which seem more appropriate for defining the route to be followed by stone fragments located in the inferior pole. We have therefore used this method to measure the IPA in our study.

In our population, we found no statistically significant differences between the two groups when comparing infundibular length and width, the length/width ratio, the IPA or the number of minor calyces (Table-1). Indeed, both in the univariate and logistic regression analyses we found that only infundibular height ($p = 0.002$) had a significant impact on calculus elimination and that it could be used to predict the success of SWL in lithiasis of the inferior pole. These results are similar to those of Tuckey et al. who, in order to simplify calculation of the renal collecting system, analyzed the height of the infundibulum, found that patients with a calyx height of < 15 mm eliminated the fragments in 95% of the cases, whereas patients with a calyx height of > 15 mm only do so in 52% of cases (15). Although this variable is easy to measure compared with others such as the IPA and it is reproducible without requiring a bevel protractor to measure it, some groups disregard it because they believe that the measurement could vary in each urography according to the patient's respiratory movements and postural changes (7). Sorensen et al. found a statistically significant difference in a wide range of infundibular height (less than 15 mm or more than 30 mm) defined for stones less than 10 mm (14). Poulakis et al. used an artificial neural network in order to determine which anatomic measurements could predict the stone free status after SWL. They found that infundibular height was one of the most important variables to predict it with an excellent reproducibility of this measurement (11). More recently, another study performed by Symes et al. proved that infundibular height is useful to predict the success rate after SWL when treating lower pole renal stones less than 20 mm (13).

Unlike Tuckey et al. (15), who used a 15 mm cut-off point to predict which patients were candidates for SWL, we analyzed all the possible cut-off points with a ROC curve, finding that the points with highest sensitivity and specificity in our population were between 22 mm and 24 mm of infundibular height. The real cut-off point in our ROC curve, with optimal sensibility and specificity, was 22.5 mm, but we reduced it to 22 mm because clinically it is very difficult to measure 0.5 mm. Using the value of 22 mm as a cut-off, in our population we found that 68.6% of patients with an infundibular height less than 22 mm were stone-free and only 35% of patients with an infundibular height higher than 22 mm were free from fragments. In agreement with Tuckey and Poulakis we suggest that this is one of the most easily and reproducible anatomic factors to measure when evaluating the lower pole and should be considered. Although

our results are promising further prospective studies comparing IVU and CT scans, with a larger number of patients are warranted to confirm our data.

CONCLUSIONS

After analyzing all the aforementioned anatomical factors, our data suggests that the height of the calyx could be used in our population to predict which patients with lithiasis in the lower calyceal group would benefit from treatment with SWL. As the parameter is easy to calculate in outpatients without the need for specific instruments, it is certainly of great interest for consideration in future studies. Although we have found a possible range of cut-off points for distinguishing between these patients, further prospective studies with a larger number of patients are required to confirm our data.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

The authors studied the influence of lower pole anatomy on the clearance of lower pole calyceal stone after extracorporeal shock wave lithotripsy (SWL). They found that only lower infundibular height of less than 22 mm was a favorable factor for a good outcome after SWL. In this study, the stone surface area was 86.1 mm2 in average. Previous studies showed that lower pole anatomy was important for the choice of treatment of lower pole stone sized 1-2 cm. I agree that the infundibular height is an easy method (cut off: 22 mm), nevertheless, several studies also demonstrated the importance of other factors such as infundibular width, infundibular length and mainly infundibulopelvic angle. Sampaio et al. (1) and Lojanapiwat et al. (2) demonstrated the effect of infundibulopelvic angle in the outcome of SWL treatment for lower pole calyceal stone sized between 1 to 2 cm (1,2). I would suggest that the combination of these factors is still important for understanding this clinical problem.

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EDITORIAL COMMENT

The purpose of this study was the prediction of stone clearance after shock wave lithotripsy (SWL) of small lower pole stones (LPS). In the time before modern endourology with flexible ureterorenoscopy and minimally invasive percutaneous nephrolitotripsy, SWL was with no doubt the treatment of choice in cases of LPS. Following the prospective randomized trials of Albala et al. (1) and Pearle et al. (2), despite their low statistical power, which were both cited in this contribution, stone free rates of SWL seem to be inferior to modern endourological approaches. Therefore, pre-procedure predictive factors are needed to increase predictive stone clearance after SWL and to customize the therapy for each patient, either SWL or an endourological procedure.

There are two principals of pre-procedure prediction, anatomical factors like skin to stone distance, calyx geometries or stone characterization like density (Hounsfield units) or dual source computed tomography.

Until now, several attempts for prediction of stone clearance have been published; however, Knoll et al. (3) showed their insufficient reproducibility by different investigators. However, infundibular height, which was previously published by Tuckey et al. (4) seems to be easily reproducible and could be one of the missing prediction factors for decision of treatment, either effective SWL or an endourological procedure. Studies comparing the infundibular height in intravenous urograms and CT scans would be needed to further see the potential of this method.

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EDITORIAL COMMENT

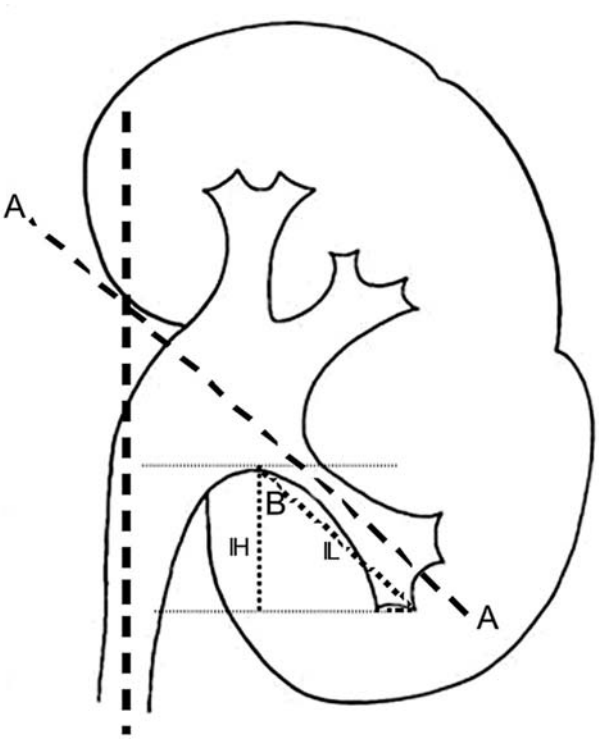
The present study focused on the role of measuring infundibular height (IH) as a predictor of success in the treatment of lower pole calyceal stones after SWL and suggests that a cutoff value of 22 mm should be used as a reference. IH is determined on intravenous pyelography. As such, contemporary imaging for the diagnosis of urolithiasis relies primarily on non-contrast CT scan imaging; therefore, the

information needed to calculate infundibular height may not be available prior to shockwave lithotripsy.

Stone free condition was determined by X-ray and ultrasonography; methods which have faded into historical significance when it comes to imaging to define outcomes in clinical research protocols.

As gender was demonstrated to impact stone-free results, a multivariate analysis controlling for this would be needed to confirm that IH remains an independent predictor.

Finally, when analyzing infundibular length (IL) and height as components of a right triangle (see figure) the IL line is approximately parallel to AA, which means that angle B approximately equals the infundibular pelvic angle (IPA).



By extending the line at the base of IH from the lowest part of the calyx to the most distal point of the calyx, we have a right triangle with IL as the hypotenuse.

Assuming that angle B equals the IPA then the formula that relates IPA, IH and IL is: cos(IPA) = IH/IL or IH = IL * cos(IPA)

Therefore, since the three measures are dependent, given any 2, one should be able to find the third. One would therefore expect that if IH is a predictor of stone clearance, the relationship between IPA and IL would also be a predictor of stone clearance.

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Perioperative Outcomes of Open Radical Prostatectomy versus Laparoscopic Radical Prostatectomy in Asian Men: Comparison of Two Initial Series by the same Surgeon

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ABSTRACT

Purpose: To compare the perioperative outcomes in 2 initial series of open radical prostatectomy (ORP) and laparoscopic radical prostatectomy (LRP) in Asian men with prostate cancer.

Materials and Methods: From March 1999 to February 2007, the first 100 consecutive patients who underwent ORP and the first 100 consecutive patients who underwent LRP by the same surgeon (SL) were assessed. Mean age, clinical stage, preoperative PSA level, Gleason score, operative time, estimated blood loss, blood transfusion rate, perioperative complications, pathological stage and margin status were compared between the 2 groups.

Results: For each 100 patients in ORP and LRP, mean age and clinical stage were not significantly different. The operative time in LRP was significantly longer than ORP (188 ± 55 versus 114 ± 31 minute, p value = 0.01). Mean estimated blood loss and blood transfusion rate in LRP was significantly lower than ORP, 521 ± 328 versus 809 ± 510 mL (p value = 0.03) and 27% versus 55% (p value = 0.01), respectively. For pathological organ confined disease, the free surgical margin rate of ORP and LRP was not significantly different (88.9% versus 91.3%, respectively, p = 0.58). There was no significant major complication in either group.

Conclusions: For initial experience by a single surgeon, LRP is comparable to ORP with no significant morbidity. LRP had longer operative time. However, LRP decreased blood loss and blood transfusion. For localized prostate cancer, free surgical margin rate of ORP and LRP was not significantly different.

Key words: *prostate neoplasms; prostatectomy; laparoscopy*

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INTRODUCTION

Radical prostatectomy has been a standard treatment for clinical localized prostate cancer. Open retropubic radical prostatectomy (ORP) has been accepted as a standard technique (1-3). For over a decade, minimal invasive surgery techniques have been widely used for prostate cancer in urology, and laparoscopic radical prostatectomy (LRP) in particular has become a standard treatment for clinically localized prostate cancer (4-6). Reported data in western countries have shown that early LRP results could be comparable to ORP in terms of operative parameters, morbidity, urinary function, sexual function and oncological outcome (4,7-9). Furthermore, several studies have shown various advantages of LRP. During LRP the structure of prostate gland, urethra, bladder, neurovascular bundle and other surrounding tissues are magnified. Thus, LRP is associated with less blood loss and blood transfusion. Patients who undergo LRP experience less postoperative pain, require fewer analgesic drugs and reduce their hospital stay. However,

LRP requires longer operative time and is more costly than ORP. Since there are few published data regarding these issues in South East Asia, this study was conducted in Thai men to compare perioperative data and pathological outcomes between LRP and ORP. To reduce variations in surgical skill and experience of the surgeon, all patients in two initial series of ORP and LRP were operated on by single surgeon.

MATERIALS AND METHODS

From March 1999 to February 2007, the first 100 consecutive patients who underwent ORP and the first 100 consecutive patients who underwent LRP by single surgeon (SL) at Siriraj Hospital, Bangkok, were retrospectively evaluated. Pathology results in all patients confirmed adenocarcinoma of the prostate gland. All patients had clinical localized (cT1 or cT2) or clinical locally advanced (cT3) prostate cancer and negative bone CT scan. In each group, most patients were diagnosed using a transrectal ultrasound guide biopsy if they had elevated prostate-specific antigen (PSA) or abnormal digital rectal examination (DRE) or both. However, some patients with previous transurethral prostatectomy (TURP) were diagnosed with prostate cancer somewhere else and referred to our hospital for further definite treatment. All treatment options were informed and decided by the patients alone. During 1999-2004, all patients in this series underwent ORP. LRP in this series was initially performed in February 2005, then, LRP was performed parallel to ORP. In 2006 and 2007, almost all patients in this series underwent LRP. All surgical procedure options were also decided by the patients themselves. All ORPs were performed using the retrograde technique described by Walsh (10). Of the 100 patients with LRP, 42 and 58 patients underwent the procedure via an intraperitoneal or extraperitoneal approach, respectively. To compare the perioperative data, morbidity and pathological outcomes between ORP and LRP, patients' age, clinical stage, preoperative PSA level, Gleason score, operating time, estimated blood loss, blood transfusion rate, perioperative complications, pathological stage and margin status were compared. Mean data were compared using the Student's t-test. Chi-square test was used for descriptive data. All data were analyzed by SPSS software program.

RESULTS

The patient characteristics of age, clinical stage, preoperative PSA level and Gleason score between ORP and LRP are shown in Table-1. Mean age and clinical stage were not different between ORP and LRP. Mean preoperative PSA level in ORP was higher than that in LRP. However, mean Gleason Score in LRP was higher than that in ORP. Of 100 patients in each group, 8 in ORP and 17 patients in LRP had previous TURP. Table-2 shows operative and pathological data in both groups. The operative time in LRP was significantly higher than that in ORP. In contrast, estimated blood loss and blood transfusion rate were significantly lower in LRP. Of 100 patients in ORP, 72 and 28 patients had pathological localized (pT2) and pathological locally advanced disease (pT3), respectively. Of 100 patients in LRP, 69 and

Table 1 – *Patient characteristics in ORP and LRP.*

	ORP	LRP	p Value
No. of patients	100	100	
Mean age (years)	68.6 (SD = 6.5)	65.5 (SD = 7.0)	0.61
Preoperative PSA (ng/mL)	18.1 (SD = 19.1)	13.8 (SD = 12.2)	0.02
Gleason score	6.5 (SD = 1.2)	7.1 (SD = 0.8)	0.01
No. clinical stage T1, T2	90	87	0.56
No. clinical stage T3	10	13	0.56

ORP = open retropubic radical prostatectomy; LRP = laparoscopic radical prostatectomy; SD = standard deviation.

Table 2 – *Operative and pathological data in 100 patients of ORP and 100 patients of LRP.*

	ORP	LRP	p Value
Operative time (min.)	114 (SD = 31)	188 (SD = 55)	0.01
Estimate blood loss (mL)	809 (SD = 510)	521 (SD = 328)	0.03
Blood transfusion (%)	55	27	0.01
Pathological localized stage (%)	72	69	0.64
Over all free margin rate (%)	73	71	0.38

ORP = open retropubic radical prostatectomy; LRP = laparoscopic radical prostatectomy; SD = standard deviation.

31 patients had pT2 and pT3, respectively. In both groups, there was no significantly different proportion of the prostate affected or a locally advanced disease. Overall free margin rate in ORP and LRP were not significant different (p = 0.38). Table-3 shows margin status in pT2 and pT3 stage between ORP and LRP. Of 72 and 69 patients with pT2 in ORP and LRP, 64 (88.9%) and 63 (91.3%) margin free, respectively. It was not significantly different (P = 0.58). In pT3, positive margin rate were high in both groups. However, it was not significantly different between ORP and LRP (p = 0.43). For pathological stage and margin status, our data showed that ORP and LRP were also not statistically different.

There were 3 complications in ORP. One patient had prolonged urinary leakage for 2 weeks and conservatively treated. Two patients had wound infection. For LRP, 5 patients required a conversion to ORP. Three patients had no progression in surgical technique for LRP due to the learning curve. All of these 3 patients were in the first 5 patients in this series. One patient had CO_2 retention during suturing of an anastomosis and needed a conversion to ORP. Another had incidental colonic cancer and also required conversion to colonic resection. There was prolonged urinary leakage in 3 patients in LRP. However, all patients were treated conservatively. One patient in LRP had urine collection in pelvic cavity due to voiding obstruction. There was no rectal injury in either group.

All patients had no preoperative incontinence in either group. After surgery, we defined incontinence status as 3 degrees according to the number of pads used for the entire day. No pad was considered as any incontinence, 1 or 2 pads were considered as incontinence and 3 or more pads were considered as severe incontinence. For 6 months, of 100 patients in ORP, 90 patients had no pad, 7 patients had incontinence that needed 1 or 2 pads. Three patients had severe incontinence that required 3 or more pads or other de-

Table 3 – *Surgical margin in pathological localized disease and pathological locally advanced disease between ORP and LRP.*

	Number of Patients		
	ORP	LRP	p Value
Localized staging	72	69	
Free margin	64 (88.9%)	63 (91.3%)	0.58
Positive margin	8 (11.1%)	6 (8.7%)	0.58
Locally advanced staging	28	31	
Free margin	9 (32.1%)	8 (25.8%)	0.43
Positive margin	19 (67.9%)	23 (74.2%)	0.43

ORP = open retropubic radical prostatectomy; LRP = laparoscopic radical prostatectomy.

vices. For 100 patients in LRP, 92 patients had no pad, 6 patients had incontinence that needed 1 or 2 pads. Two patients had severe incontinence that needed 3 or more pads or other devices. As regards potency, it was difficult to evaluate in this series. Bilateral nerve sparing procedure did not performed in the patients with high-risk cancer such as cT3, PSA higher than 10 ng/mL, Gleason score 8 or above, patients who had previous impotence or patients who did not have sexual interest. In addition, end point of this study was short for perioperative period. Thus, our data regarding potency was limited. However, several of the younger patients with bilateral nerve sparing had potency after surgery.

COMMENTS

ORP has been used as a standard technique for clinical localized prostate cancer (1-3). Since minimal invasive surgery has increased worldwide, LRP has been increasingly performed and has become a standard technique in many centers (4-6). Our hospital also uses LRP as a standard operation for clinical localized prostate cancer. A number of reported data suggest that LRP has several advantages such as small incision, fast recovery, less pain, magnified picture for accurate dissection and reduced blood loss. However, LRP is a difficult procedure that needs surgical skill and long learning curve (7,11). Outcomes of radical prostatectomy are also depended on several factors including surgical skill and experience of the surgeon and surgical team. There are many reported series comparing data between ORP and LRP in the literature (4,7-9), the majority published in the western countries. Our study comparing ORP and LRP was limited to the South East Asia region. It was retrospectively carried-out to evaluate ORP and LRP in Thai men. To exclude variation of surgical skill and experience of surgeon, the first 100 cases of ORP and the first 100 cases of LRP performed by a single surgeon were compared.

Each cohort group showed the same patient characteristics except for preoperative PSA. Preoperative PSA in our series was higher than other series (8,9,11). At present, there has been no official prostate cancer screening program in Thailand. In the past, most patients who had PSA testing were men with lower urinary tract symptoms (LUTS) and diagnosed as benign prostatic hyperplasia (BPH). Since there has been more prostate cancer awareness in recent years, PSA testing was used more in men without LUTS or BPH. More patients presented with abnormal PSA regardless of LUTS or BPH. Therefore, more patients have presented with lower PSA in recent years. For these reasons, patients in ORP group who were diagnosed in the past had higher PSA than patients in LRP group who presented in recent years. However, preoperative PSA in both groups were higher than in the western countries. Another reason was that the treatment option for prostate cancer was decided by the patients, and most Thai patients preferred radical prostatectomy even when there were high risks (PSA > 10 ng/mL).

Our data showed that LRP had significant less blood loss and blood transfusion than ORP because LRP had magnified structure of organs and surrounding tissues resulting in more accurate dissection. However, LRP had longer operative time. There was no mortality. The morbidities could be managed safely. Incontinence rate was comparable to other series (4-7). This study also concluded that LRP was a safe procedure even in the initial period.

The proportion of pathological localized disease was not different in both groups. Approximately 70% of the patients were organ confined disease and approximately 30% were locally advanced disease. For pathological organ confined disease, free margin rates in ORP and LRP were 88.9% and 91.3%, respectively, which were comparable to other series (8,9). This was not different between ORP and LRP. For pT3 disease, positive margin were high in both groups and not significantly different. Our data showed that surgical technique between ORP and LRP to remove cancer in terms of positive surgical margin were not different. Both ORP and LRP in our series achieved high free margin rate in organ confined disease. In terms of pathological results, we considered that our surgical technique of LRP was appropriate to be considered a standard technique used for organ confined disease. In contrast, both ORP and LRP could not achieve the accepted free margin rate in locally advanced disease. High positive margin rate in pT3 might be due to several factors such as high preoperative PSA, clinical T3 stage or surgical technique in the learn-

ing curve period. The most common site of positive margin was apex. It requires experience to completely remove tumors that were located beyond the prostate gland with preserving enough urethral length for continence. As mention above, the proportion of pT3 in our series was almost one-third. Thus, overall positive margin rates in both groups were higher than other series. However, the overall free margin rate between ORP and LRP was not different. Since our data only concerns a limited follow-up period, the outcomes for cancer control will require long term evaluation.

All data of perioperative surgical parameters, morbidities and pathological results showed that LRP was comparable to ORP even during the period of the initial series for the surgeon. Our results suggest that LRP could be considered a standard technique as ORP for clinical localized prostate cancer in Asian men.

The procedure of radical prostatectomy is an issue that needs experiences of surgical skill and number of cases to overcome the learning curve. For ORP, the bleeding and blood transfusion rate was high. At the beginning, almost patients needed a blood transfusion. When we had more experience, bleeding and blood transfusion were reduced. For LRP, it was a very difficult procedure when we performed in the early period. Three cases of LRP that need conversion to ORP because of no progression were in the beginning period. When we had more experience, the operating time decreased from 5 hours to 2-3 hours and estimated blood loss and blood transfusion rate greatly decreased. The important factor to improve skill is to continuously perform the procedure. In Thailand, most cases of radical prostatectomy are performed at the referral center such as the university hospital. At present, ORP is increasingly performed in many hospitals. In contrast, LRP is still limited to few hospitals. Thus, most patients with clinical localized prostate cancer are referred to the university hospital. In Thailand, even the prevalence of prostate cancer is not as high as those in the western countries; more prostate cancer awareness in recent years has caused more clinical localized cancer to be detected. In addition, our university hospital is a medical center where the majority of patients with prostate cancer are referred to and therefore, we continue perform LRP on a regular basis.

CONCLUSIONS

For initial experience by a single surgeon, LRP is comparable to ORP without significant morbidity but LRP had a longer operative time. However, LRP decreased blood loss and blood transfusion. For localized prostate cancer, free surgical margin rate of ORP and LRP was not significantly different. With increasing experience the laparoscopic technique should be considered a feasible procedure for patients with prostate cancer.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

The paper presents an interesting retrospective study relevant to countries where daVinci robot is not widely available. In fact, it seems to be an honest report of two series of radical prostatectomies that started at different times. The author has performed open surgery for the first time in 1999 and laparoscopic procedure in 2005. After performing open radical prostatectomy for some years, he began performing it laparoscopically in elective patients. The low volume of this surgery (200 in 8 years) makes its mastery harder. Finally, the authors developed a preference for laparoscopy despite similar rates of positive margins and functional results. It would be interesting to know what the surgeon's previous experience in laparoscopy was before he started doing radical prostatectomy. Also, we could not follow the evolution of the learning curve neither in open nor in laparoscopic surgeries. The operative time was relatively short but the bleeding and the transfusion rates were higher than those in other series were. Perhaps the final message of the article is that most urologists that perform open radical prostatectomy who have had the perseverance to climb up the learning curve of radical prostatectomy eventually prefer doing it laparoscopically.

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EDITORIAL COMMENT

Laparoscopic radical prostatectomy (LRP) is increasingly performed at specialized centers worldwide. With gathering experience, the laparoscopic technique has been shown to be feasible and reproducible (1).

The laparoscopic approach offers the advantages of laparoscopic surgery as less postoperative pain, fewer analgesics drugs and early mobilization. The magnification of the surgical field, allow a clear operative field with better view during the dissection of the neurovascular bundles and the urethro-vesical anastomosis.

The authors show in this paper a longer operative time with the LRP. However, LRP decreased blood loss and blood transfusion. For this population of localized prostate cancer, free surgical margin rate of ORP and LRP was not significantly different.

Outcomes of radical prostatectomy are dependent on several factors including surgical skill and experience of surgeon and surgical team. Besides, radical prostatectomy requires a sufficient number of cases to overcome the learning curve. It should be learned within an intensive teaching program (2).

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. Multicenter studies with longer follow-up are necessary.

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EDITORIAL COMMENT

The authors present the results of a nonrandomized series within the learning curves of both radical retropubic prostatectomy and laparoscopic radical prostatectomy. The results of the laparoscopic approach are surprisingly good for the first 100 cases, even in terms of surgical time and urinary continence. This fact reflects a special skill with the laparoscopic technique acquired by the single surgeon before the beginning of this series and, at the same time, a previous huge experience with open radical prostatectomy, or a bias during the selection of the patients.

The authors should explain the extremely high rates of blood transfusion in both groups, respectively 27% (LRP) and 55% (ORP). These numbers are not compatible with the contemporary data from the literature.

The authors could give us their results and their position about the differences between extraperitoneal (58 cases) and transperitoneal (42 cases) laparoscopic surgery.

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Reducing the Number of Sutures for Vesicourethral Anastomosis in Radical Retropubic Prostatectomy

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ABSTRACT

Objectives: To prospectively evaluate the outcome of using a two-suture technique for the vesicourethral anastomosis (VUA) during radical retropubic prostatectomy (RRP).
Materials and Methods: Two groups of 50 patients each underwent nerve-sparing RRP for localized prostate cancer by one surgeon. In one group, the vesicourethral anastomosis was performed using 2 Vicryl 2-0 stitches placed at the 3- and 9-o'clock positions and in the other group 6 Vicryl 2-0 stitches were placed at the 2-, 4-, 6-, 8-, 10- and 12-o'clock positions. The intraoperative and perioperative parameters analyzed were time to perform the VUA, time to remove the drain and hospitalization. The rate of incontinence, anastomotic stricture and erectile function were included in the outcome analysis.
Results: The anastomotic time differed statistically between the 2 groups (mean 3.3 minutes for the 2-suture group and 10.5 minutes for the 6-suture group, $p < 0.0001$) with similar periods of drain removal (mean 3.12 days for the 2-suture group and 3.45 days for the 6-suture group; $p = 0.13$) and hospitalization (mean 4.66 days for the 2-suture group and 5.3 days for the 6-suture group; $p = 0.09$). The functional outcome was excellent for the 2-suture group with no patient suffering from incontinence or anastomotic strictures 1 year postoperatively, while in the 6-suture group there were 2 patients (4%) suffering from incontinence (2 underwent sling procedure) and 1 patient suffered from anastomotic stricture.
Conclusion: The low number of sutures in the 2-suture VUA technique reduces operating times, does not influence perioperative and intraoperative parameters and results in excellent functional outcome.

Key words: *prostatic neoplasm; prostatectomy; anastomosis, surgical; sutures; treatment outcome*
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INTRODUCTION

Radical retropubic prostatectomy (RRP) is one of the treatment modalities recommended for clinically organ-confined prostate cancer. The better understanding of pelvic anatomy has led to the development of the anatomic approach of RRP (1) and to the reduction of specific complications of the operation such as incontinence, anastomotic stricture and impotence.

One of the critical steps of the operation that may influence the rate of postoperative complications is the anastomosis of the bladder to the urethral stump. Historically, the number of six sutures was described by Walsh (1) to be used for the vesicourethral anastomosis (VUA). However, this number may vary from four (2) to eight sutures, according to other experienced surgeons, with adequate functional results (3). A reduction in the number of sutures used in order to perform the VUA in radical prostatectomy

is now becoming important in the laparoscopic era where intracorporeal suturing is difficult and intraperitoneal leak could be a problem. We examined the feasibility of an interrupted two-suture vesicourethral anastomosis technique and its effect on the outcome of prostate cancer patients after open radical retropubic prostatectomy.

MATERIALS AND METHODS

From September 2005 to October 2006, we prospectively evaluated 100 patients, divided randomly into two groups of 50 patients each, by consecutive allocation to each group, who underwent nerve-sparing RRP by a single surgeon, after obtaining institutional review board approval. Patients who had undergone preoperative androgen ablation, local radiotherapy, previous transurethral or suprapubic resection of the prostate or underwent non nerve-sparing RRP were excluded from the study.

All patients underwent bilateral pelvic lymphadenectomy and standard nerve-sparing RRP as described by Walsh (1). The bladder neck was preserved and bladder neck mucosal eversion was performed routinely using 4 to 6 circumferential absorbable sutures 3-0. In one group the vesicourethral anastomosis was performed using 2 Vicryl (Ethicon, NJ, USA) 2-0 stitches placed at the 3- and 9-o'clock positions and in the other group 6 Vicryl 2-0 stitches were placed at the 2-, 4-, 6-, 8-, 10- and 12-o'clock positions. The VUA was carried-out on a 22F 3-way Couvelaire catheter, which was removed on the 10th postoperative day without performing a cystogram. Two drains were also routinely placed laterally to the anastomosis. They were removed when daily drain output was less than 50 mL.

The following intraoperative and postoperative parameters were recorded: time to perform VUA, blood loss, pre-and postoperative hemoglobin, drain output, time to drain removal and consequent transfusions. Follow-up consisted of visits every 3 months for 1 year, during which physical examination was performed and PSA values measured. All patients were encouraged to execute pelvic floor exercises (Kegel) (4) and phosphodiesterase-5 (PDE5) inhibitors were also administered early postoperatively (5). Continence was evaluated by the number of pads used daily as reported by the patients during the follow-up visits. They were defined as continent when no more than one pad daily was required (6).

The statistical analysis was performed by Student's t-test for quantitative data and the chi-square test for categorical data. Results were considered statistically significant at $p \leq 0.05$.

RESULTS

Patient characteristics such as age, PSA value, body mass index, prostate volume measured by transrectal ultrasound and Gleason score are presented in Table-1.

Table 1 – *Patient characteristics.*

	2-suture VUA	6-suture VUA	p Value
Mean age (range)	64.6 years (52-74)	64.1 years (49-76)	p = 0.82
Mean PSA (range)	8.44 ng/mL (3.5-19.58)	8.59 ng/mL (4-28.2)	p = 0.86
Mean Gleason score (range)	6.19 (3-9)	6.15 (3-8)	p = 0.94
Mean BMI (range)	25.7 (21-38)	25.9 (19-40)	p = 0.91
Mean TRUS volume (range)	21.8 cm^3 (16-38)	22.2 cm^3 (15-42)	p = 0.77

VUA = vesicourethral anastomosis; BMI = body mass index; TRUS = transrectal ultrasound.

The analysis of the intraoperative parameters revealed a mean time to perform the vesicourethral anastomosis (VUA) of 3.3 minutes for the 2-suture technique and 10.5 minutes for the 6-suture technique (Table-2). Urinary leakage occurred in 4 patients (8%) in each of the two groups while the mean volume was 1125 mL for the 2-suture technique compared with a significantly less mean volume of leakage of 980 mL for the 6-suture technique. Urinary leakage in both groups subsided spontaneously with patient mobilization and all drains in these patients had been removed by the 3rd or 4th postoperative day, thus all patients were discharged without drains.

During the postoperative course the mean time to ambulation was 1 day for the 2-suture technique and 1.02 days for the 6-suture technique, the mean time to oral intake was 1.22 (range 1-4) days and 1.15 (range 1-3) days respectively. Timescale to drain removal and patient discharge did not differ statistically between the two groups (Table-2).

No significant postoperative bleeding was observed as only 2 patients (4%) were transfused with 3 blood units in total in each group postoperatively.

Regarding the 2-suture technique, no patient suffered from incontinence 1 year postoperatively, while with the 6-suture technique, 2 (4%) patients were incontinent in the same period and a male sling was placed successfully. No patient suffered from anastomotic stricture with the 2-suture technique while 1 patient suffered from stricture with the 6-suture technique, which was endoscopically treated (Table-2).

COMMENTS

The creation of the VUA is a crucial step in RRP since it affects future outcomes and thus the quality of life of such patients postoperatively. It seems that prevention of anastomotic stricture (2) and urinary continence (7) depends on a well-healed vesicourethral anastomosis. The general principle to achieve this, regardless of the anastomotic technique used, is a watertight, tension-free anastomosis with mucosal-to-mucosal coaptation and proper urethral alignment (8).

Recently, a VUA technique using two interrupted sutures with equal outcomes while offering reduced anastomotic time was reported (6). The task of performing a 2-suture technique for the VUA is not only convenient for open RRP but may also simplify the procedure for the laparoscopic approach since suturing during laparoscopy is more challenging. Leakage was significantly higher in the 2-suture

Table 2 – *Intraoperative and postoperative parameters as well as functional outcome.*

	2-suture VUA	**6-suture VUA**	**p Value**
Mean time to VUA (range)	3.32 min (2.9-4.2)	10.5 min (7.5-14)	$p < 0.0001$
Mean total urinary leakage (range)	1125 mL (600-1500)	980 mL (700-1310)	$p = 0.01$
Mean EBL (range)	454.17 mL (200-1000)	733.63 mL (300-2500)	$p = 0.001$
Mean time to ambulation	1 day	1.02 day	$p \leq 1$
Mean time to oral intake (range)	1.22 days (1-3)	1.15 days (1-3)	$p = 0.33$
Mean time to drain removal (range)	3.12 days (2-5)	3.45 days (2-6)	$p = 0.13$
Mean hospital stay (range)	4.66 days (3-10)	5.3 days (3-11)	$p = 0.09$
Incontinence at 12 months	0 patients (0%)	2 patients (4%)	$p = 0.24$
Anastomotic stricture	0 patients	1 patient	

VUA = vesicourethral anastomosis; EBL = estimated blood loss.

technique; however, it stopped spontaneously with ambulation and was drained effectively, thus resulting in no patients with incontinence or anastomotic stricture. Our two-suture technique for the VUA is faster and less challenging than using a four (2), six (1) or eight-suture (3) or even a running suture (9) technique since it is obvious that by using more sutures is more time-consuming and complicated. Some surgeons place their sutures in the urethra before dividing it completely and leave them on the surgical table until the bladder neck is ready for the VUA; while others place their sutures creating the VUA after the prostate has been removed. In the first case sometimes sutures become entangled increasing the surgical time. It is evident that by using only two sutures entanglement is more difficult and disentanglement easier. Furthermore, in contrast to a recent study using the two-suture technique (6) the placement of sutures in the 3 and 9 o'clock positions instead of the 6 and 12 o'clock, avoids the rectum and the rectourethralis muscle dorsally and branches of the Santorini plexus anteriorly.

Moreover, in the present series preservation of the bladder neck was selected since earlier return to continence and a reduction in the stricture rate have been reported when using such technique (10). We also everted the bladder mucosa permitting a close coaptation with the urethral mucosa and tried to avoid interposition of perivesical fat when tying the sutures (11).

In the present series no patient with the 2-suture and 1 patient with the 6-suture technique developed an anastomotic stricture, which rates vary in the literature from 0.5% to 32% (12), despite having 4 patients in each group with urinary leak in the early postoperative period, which has been described as a risk factor (13) for stricture formation. The incidence of urinary leak for the 2-suture technique was higher compared with the 6-suture technique in accordance with other studies (6). In all of these patients the leak ceased spontaneously with ambulation and an unobstructed urethral catheter. On the contrary, it seems that the degree of tightness of the anastomosis (9) with a compromised vascular supply to the bladder neck and the urethra is a predisposing factor for stricture formation, thus by using two sutures we avoid such tightness. Furthermore, we used a 3-way wide catheter of 22F without traction, in order to achieve healing of the suture line since it has been proven that the incidence of anastomotic stricture is reduced with a wider caliber of the anastomosis (14). A large bore catheter results in better drainage, which decreases the potential for leakage. Postoperative bleeding was also minimal in our patients, thus avoiding another risk factor for stricture formation. By using drains, especially large ones in the early postoperative period, better removal of fluid or blood from the anastomotic site is achieved, in order to avoid fibrosis and stricture formation.

The rates of incontinence after RRP have been reported from 2.5% to 87% (15), yet a 12-month period is necessary before defining a patient's continence status (16). Several risk factors have been reported to contribute to continence after RRP such as patient age, disease stage, surgical technique, preoperative continence and previous transurethral resection of the prostate (17). In our series the rate of incontinence was very low, consistent with other reports (9) and it is noteworthy that no patient suffered from incontinence 1 year after the operation with the 2-suture technique while 2 patients were incontinent with the 6-suture technique.

In order to preserve continence, the membranous urethra, the sphincter mechanism and its innervations as well as the anastomotic blood supply should be preserved. The "continence nerves" seem to be damaged during blunt dissection of the posterior periurethral tissues near the junction of the levator ani muscle and during placement of the anastomotic sutures at the 5- and 7-o'clock positions (6). By placing sutures in the 3- and 9-o'clock positions we can avoid such nerves. Additionally, by using the nerve-sparing procedure we improved our continence rates (18), which are possibly attributed to the meticulous dissection of the nerves from the apex of the prostate instead of the preservation of the neurovascular bundle. Furthermore, preservation of the bladder neck especially of its circular fibers, as in this series of patients, contributes to return of continence (19).

In this initial number of patients we removed the catheter after 10 days although being aware of the accumulating reports of early catheter removal (20). Nevertheless, we must be aware that there are

differences in the surgical technique and the number of sutures used for the VUA. Prospective comparative studies with several techniques for VUA are required, in order to confirm the superior results of a 2-suture technique. However, we must acknowledge that these 50 patients, with this specific surgical technique of reduced number of sutures for the VUA, had excellent outcome with minimal complications compared with the same number of patients with a 6-suture technique, thus, proving effective, less challenging and convenient for use in open RRP. We must also acknowledge that in our study patients were discharged in their majority between the 4th and 5th postoperative day, due to special circumstances existing in our country (long distance from permanent residence, National Health System environment, no pressure by insurance companies, etc).

CONCLUSION

The reduced number of sutures used for the VUA in the present study reduced surgical time safely, is easier to perform and achieved excellent functional outcomes. Although urinary extravasation was higher in the intraoperative period, it was managed conservatively and stopped spontaneously having no effect on stricture formation. The reduced number of sutures for the VUA seems to have a lower incidence of incontinence and anastomotic stricture resulting in minimal late complications after RRP.

CONFLICT OF INTEREST

None declared.

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Uni- vs. Multiloculated Pelvic Lymphoceles: Differences in the Treatment of Symptomatic Pelvic Lymphoceles after Open Radical Retropubic Prostatectomy

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ABSTRACT

Purpose: To evaluate the treatment of symptomatic pelvic lymphoceles (SPL) after performing radical retropubic prostatectomy (RRP) and pelvic lymphadenectomy (PLA) simultaneously.
Material and Methods: We analyzed, in a retrospective study, 250 patients who underwent RRP with PLA simultaneously. Only patients with SPL were treated using different non- and invasive procedures such as percutaneous aspiration, percutaneous catheter drainage (PCD) with or without sclerotherapy, laparoscopic lymphocelectomy (LL) and open marsupialization (OM).
Results: Fifty-two patients (21%) had postoperative subclinical pelvic lymphoceles. Thirty patients (12%) developed SPL. Fifteen patients with noninfected uniloculated lymphocele (NUL) healed spontaneously after performing PCD. The remaining seven patients required sclerotherapy with additional doxycycline. After performing PCD, NUL healed better and faster than noninfected multiloculated lymphocele (NML) (success rate: 80% vs. 16%, respectively). Twenty-seven percent of patients treated initially with PCD, with or without sclerotherapy had persistent lymphocele. All patients were successfully treated with LL. Only one patient had an abscess as a major complication of a persistent SPL after PCD and sclerotherapy and was treated via an open laparotomy.
Conclusions: Symptomatic NUL can be treated using PCD with or without sclerotherapy. If this therapy fails as first-line treatment, laparoscopic lymphocelectomy should be considered within a short period of time in order to achieve successful treatment. NML should be treated using a laparoscopic approach in centers where this type of expertise is available. Infected lymphoceles are drained externally. In these cases, percutaneous or open external drainage with adequate antibiotic coverage is preferable.

Key words: *prostatic neoplasms; prostatectomy; pelvis; lymph nodes; lymphoceles; laparoscopy*
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INTRODUCTION

A lymphocele, also known as a lymphocyst, is a collection of lymphatic fluid occurring as a consequence of surgical dissection and inadequate closure of afferent lymphatic vessels. In the literature, an incidence of 0.5-10% of patients treated by radical prostatectomy having symptomatic pelvic lymphoceles (SPL) postoperatively has been reported (1-3).

Pelvic lymphadenectomy (PLA) is frequently performed simultaneously with radical retropubic prostatectomy (RRP) to determine lymph node status (4). A surgical approach is indispensable since to date no imaging study can compare with PLA to detect the

presence of metastasis (5,6). However, this potential benefit must be weighed against the additional morbidity and costs associated with PLA.

To our knowledge there are only few up-to-date studies focusing on the complications associated with PLA after RRP. Therefore, we were prompted to retrospectively analyze our data of postoperative SPL and the corresponding treatments to determine which procedure could be the most effective.

MATERIALS AND METHODS

Data on 250 patients who underwent RRP between January 2005 and December 2007 were collected. Patients were followed-up for a minimum of 6 months.

A limited or standard PLA was routinely performed after an open RRP. Our standard pelvic lymphadenectomy involved the dissection and removal of lymphatic tissue from the level of the external iliac vein to the obturator nerve, extending proximal to the common iliac artery bifurcation and distal to the proximal femoral canal to include the node of Cloquet. We did not perform an extended pelvic lymphadenectomy, which removes the lymphatic tissue surrounding the internal iliac vein and presacral region. After completing the surgery 2 closed suction drains were placed, each one laterally to the bladder, in relationship with the area of pelvic lymph node dissection. All patients received perioperative antibiotics and low molecular weight heparin after RRP.

In order to diagnose pelvic lymphoceles we routinely performed pelvic ultrasound after RRP and PLA. Pelvic ultrasound studies were performed as standard procedure during the first 10 days after RRP at least three times in each patient. In patients in whom pelvic lymphoceles were found, we performed daily ultrasound controls to check the progression or resolution of the fluid collections. Pelvic lymphoceles were defined as a pelvic fluid collection of more than 50 mL after drainage removal. Persistent lymphorrhea (PL) was diagnosed when catheter outputs exceeded 50 mL per day after 3 days of surgery. In these cases, we performed microbiological analyses of the pelvic fluid collections. Fluid collections with creatinine levels similar to serum were treated as lymphoceles. Cystograms were performed to distinguish between an anastomotic leak and a lymphocele. Doppler lower extremity studies were performed in all patients with signs and/or symptoms of complicated lymphoceles compressing the iliac veins. In major complicated pelvic lymphoceles with or without infections, we performed a CT scan or MRI.

The symptoms of this collection depended on the size and presence of infection. Patients with SPL may present a visible or palpable pelvic mass. Symptoms or signs may be a result of venous compression resulting in unilateral leg edema, leg pain and deep vein thrombosis. Fever and chills should suggest secondary infected pelvic lymphoceles.

PL and SPL were evaluated by controlling the fluid drainage per day ($\leq$ 50 mL/day or $\geq$ 50 mL/day) or the size after drainage removal ($\leq$ 50 mL. or $\geq$ 50 mL), respectively.

Treatment options also depended on other factors such as position, loculations and the recurrence of the collections. Noninfected uniloculated lymphoceles (NUL) were primarily treated using percutaneous catheter drainage (PCD) with or without additionally sclerotherapy. Noninfected multiloculated lymphoceles (NML) and persistent lymphoceles after PCD with or without sclerotherapy were treated using laparoscopic lymphocelectomy (LL).

SPL were treated initially with PCD. Percutaneous drainage was performed after insertion of an 8 to 14F pigtail catheter using ultrasound guidance. The catheter was sutured in place and daily output was recorded. Resolution of fluid collection was determined by follow-up ultrasound and clinical symptoms.

PL was treated initially with additional sclerotherapy for a maximum of 10 consecutive days. Sclerotherapy was performed with doxycycline (40 mg/day) instillated through the drainage (drain after RRP or drain after percutaneous drainage) using an aseptic technique. Lymphocele recurrence after one course of sclerotherapy was not managed with a second attempt using these sclerosant agents. If this therapy failed, we occluded the drainage for 24 hours to control, with ultrasound, the size of the lymphatic collection. We removed the catheter when the collection remained equal and did not increase. In these cases with the growing size of the lymphatic cavity,

as well as recurrence of lymphocele or with PL after PCD and sclerotherapy we performed a LL.

Laparoscopic lymphocelectomy was performed as described by McCullough et al. using a 3 or 4-port technique depending on whether the approach was uni or bilateral (7).

Open laparotomy was only performed in rare cases with persistent lymphocele after percutaneous and/or laparoscopic approaches failed, and also in major complications of the pelvic lymphoceles such as infections, abscess or acute bleeding after using other techniques.

RESULTS

Three experienced surgeons performed 250 RRPs with limited PLA. The median number of lymph nodes removed was 12.5 (r: 1-42).

Fifty-two patients (overall rate: 21%) had subclinical pelvic lymphoceles after RRP (Ultrasound volume range: 50-300 mL). Forty patients developed unilateral lymphoceles and only 12 bilateral. Thirty patients (23 unilateral/7 bilateral) (overall rate: 12%) developed SPL. In 15 cases after PCD, there was spontaneous resolution of the symptoms and they were treated using routine ultrasound surveillance. The remaining fifteen patients had PL and were treated with PCD and sclerotherapy in 7 cases. Another 3 patients were treated successfully using LL after a combined PCD-sclerotherapy failed. In other 4 cases LL was performed after PCD without sclerotherapy failed. In only one patient we performed an open laparatomy because of an infected complicated lymphocele (Table-1).

Patients with NUL who underwent PCD and sclerotherapy as first-line-treatment had a higher success rate compared to those with a NML (80% vs. 16%, respectively) (Table-2).

Twenty-seven percent of patients who were initially treated with PCD with or without sclerotherapy had a PL. All of them (100%) were successfully treated with laparoscopic marsupialization and intraoperative drainage removal.

We also observed that those patients treated successfully with PCD and adjuvant sclerotherapy required additional days of treatment to eliminate the persistent lymphorrhea compared to those initially treated with LL (average of 9.5 days of treatment vs. 1 day, respectively).

In a small group of patients (n: 4) after performing PCD we did not instill sclerosing agents in the lymphatic cavity. In these cases we decided to directly perform LL due to a persistent lymphorrhea. In all these patients we achieved good results with no recurrences of lymphoceles after this approach.

Table 1 – *Pelvic lymphoceles after pelvic lymphadenectomy and RRP.*

Initially asymptomatic pelvic lymphoceles (Uni/Bilateral) 1n / 2n (overall (%))	40/12 (20.8)
Persistent / progressed symptomatic pelvic lymphoceles (Uni/Bilateral) 1n/2n (overall (%))	23/7 (12.0)
Spontaneously regressed pelvic lymphoceles with PCD alone	15 (50.0)
Persistent symptomatic pelvic lymphoceles after PCD	15 (50.0)
PCD with sclerotherapy	7 (46.7)
Laparoscopic marsupialization of pelvic lymphoceles after a failed combined PCD-sclerotherapy	3 (20.0)
Laparoscopic marsupialization of pelvic lymphoceles without using sclerotherapy	4 (26.7)
Open laparotomy	1 (6.6)

RRP = radical retropubic prostatectomy; PCD = percutaneous catheter drainage.

Table 2 *– Classification of symptomatic pelvic lymphoceles and the results after performing percutaneous catheter drainage (PCD).*

Patients with Symptomatic Pelvic Lymphoceles	N = 30	N of Persistent Lymphoceles after Percutaneous Catheter Drainage (%)
Noninfected uniloculated lymphoceles	25	4 (16.0)
Noninfected multiloculated lymphoceles	5	4 (80.0)
Infected lymphocele	1*	1 (100.0)

** After performing a PCD in a noninfected uniloculated lymphocele, one patient developed an infected lymphocele.*

Open laparotomy was performed because of an abscess as a major complication of a symptomatic secondary infected lymphocele. After removal of the infection the patient had no further complications.

As major complication there were 2 patients (overall rate: 0.8%) who developed a deep venous thrombosis and leg edema. The presence of pulmonary emboli was not observed either radiographically or scintigraphically.

COMMENTS

In our data a high incidence (21%) of subclinical lymphoceles after PLA and RRP was observed. However, our rate was lower than that originally obtained when any sonographically or radiographically detected lymphocele was considered (range: 27-61%) (8,9). Despite an incidence of 21%, in the current study the overall rate of clinically significant SPL after PLA and RRP was 12%. This observation is in agreement with the results described by other series (3,10-12). Pepper (3), Solberg (8) and Campbell (10) reported symptomatic or clinically significant lymphoceles in 3.5%, 2.3% and 1.6% of patients, respectively.

Another relevant consequence of lymphoceles is the significantly higher incidence of re-intervention. In our study approximately 50% of all re-interventions performed in patients with prostatectomy were related to lymphocele management. In a recent study by Musch et al. these authors described similar results (4).

Symptomatic lymphoceles can be managed initially by PCD with or without instillation of sclerosing agents, such as tetracycline, ampicillin, ethanol, doxycycline or povidone-iodine (1,3). If the lymphocele is nonloculated, sclerosant therapy may be attempted (13). A multiloculated lymphocyst as shown in our study has more chances to recur under sclerotherapy because of the multiple cysts in the lymphocele cavity.

However, lymphocele recurrence rates are high: 50 to 100% (14) after simple aspiration and 10 to 15% (15) following sclerosant therapy. In our data we found lymphocele recurrence in 27% of patients treated initially with PCD with or without sclerotherapy. In our experience percutaneous sclerotherapy is associated with a low success rate and possible contamination of the lymphocele cavity. In the best case scenario Teruel et al. (15) described successful sclerotherapy using long-term percutaneous catheter drainage and at least two daily instillations of the sclerosant agent for an average of 25 days (up to a maximum of 45 days). Contrary to this concept we performed a short-term sclerotherapy for no more than 10 consecutive days. It may be possible that this once daily short-term therapy was the cause of a higher lymphocele recurrence in our data compared to other studies.

However, the long-term treatment of PCD to achieve higher success rates, prompted us to use more frequently the laparoscopic marsupialization of lymphocele, which was successful in all patients. In the literature more than 90% success was reported after peritoneal marsupialization (3,16). Pelvic lymphoceles appear to be suited ideally for drainage by laparoscopic techniques. The bulging wall of the lymphocele cavity is usually readily apparent laparoscopically. We did not routinely perform omentoplasty during laparoscopic lymphocelectomy. Disadvantages of this technique include the requirement for a gen-

eral anesthetic, and surgical trauma compared to a percutaneous approach. However, we consider that a decreased analgesic requirement, shorter hospitalization and a more rapid recovery are advantages to more frequently perform laparoscopy and therefore this approach should be considered as the standard therapy for a noninfected symptomatic lymphocele when the percutaneous sclerotherapy fails as first line-treatment. We suggest that when SPL persists, having previously attempted a noninvasive procedure, then after a short period of time a laparoscopic intraperitoneal drainage approach should be performed to avoid a secondary infection of the lymphocele cavity or an unsuccessfully extended time of noninvasive therapy.

Post-laparoscopy recurrence warrants open surgical marsupialization with or without omentoplasty (13).

Symptomatic infected lymphoceles require meticulous imaging surveillance (Ultrasound or CT scan control) and more invasive therapy is needed if major complications such as septicemia, fever ≥ 39.5°C, progression of an infected lymphocele or abscess occur. In some cases PCD can be attempted. As regards these complications some studies remain controversial. There are studies reporting a high recurrence rate after performing percutaneous drainage, whereas other authors report good results. We believe that a percutaneous approach should be performed in patients who are stable and have a localized controlled infected lymphocele. If this approach fails an open technique should be performed.

Although we performed a limited PLA instead of an extensive technique on all patients in our study, we obtained a significantly high median number of pelvic lymph nodes (median No. 12.5 lymph nodes per PLA). According to other studies the risk of lymphocele is significantly higher as the number of removed lymph nodes increases (1). This could possibly explain our higher incidence of pelvic lymphoceles compared with other data.

We suspect that in some patients the use of 2 closed suction drains instead of drainage without suction may have increased the incidence of pelvic lymphoceles reported in our study. However, further studies should be performed in order to confirm this suspicion.

Another promoter of lymphoceles in our study population might have been the standardized perioperative administration of low dose heparin for thromboembolism prophylaxis, in accordance with German Association of the Scientific Medical Societies Guidelines. Bigg and Catalona (17), and Tomic et al. (18) identified low dose heparin as a factor causing increased lymph secretion and a higher rate of lymphocele formation. In our patients heparin was administered exclusively subcutaneously into the upper arm to avoid increased lymph secretion in the pelvis (19).

CONCLUSIONS

Simple percutaneous aspiration should be used only for diagnostic purposes when indicated.

In our experience percutaneous catheter drainage with sclerotherapy is associated with a low success rate, need for a long period of treatment to achieve success and possible contamination of the lymphocele cavity. However, PCD with sclerotherapy could be attempted in patients with nonloculated symptomatic lymphoceles as first line treatment.

Our data suggest that laparoscopic lymphocelectomy appears to be safe and effective, with minimal postoperative morbidity and a low recurrence rate. Therefore, if percutaneous catheter drainage with or without sclerotherapy fails as first-line treatment, laparoscopy marsupialization of pelvic lymphocele should be considered within a short period of time. In some specific cases, as in multiloculated lymphoceles, laparoscopic lymphocelectomy should be considered as first-line treatment at centers where this type of expertise is available.

When infected lymphoceles are drained externally, percutaneous or open external drainage with adequate antibiotic coverage should be performed.

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EDITORIAL COMMENT

The article is an excellent clinical paper and should be read by all clinicians who perform pelvic lymphadenectomies because it demonstrates the good clinical practice considering the handling of pelvic lymphoceles. We share similar experience with laparoscopic treatment of lymphoceles and prefer this treatment because of his almost universal and immediate efficiency.

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EDITORIAL COMMENT

The authors deserve praise for this very interesting retrospective study about the occurrence of lymphoceles after radical prostatectomy with associated pelvic lymphadenectomy. The occurrence of 21% (52 patients) of lymphoceles detected by abdominal ultrasound, of which 12% (30 patients) with symptomatic lymphoceles, is superior to the average reported in the literature in recent years (1), which is probably a reflection of a stricter definition adopted by the authors instead of a greater occurrence in comparison to what was obtained by other authors.

The use of laparoscopic drainage was relatively low - 7 cases -, all with good evolution, which is coherent with the previously published experience concerning the laparoscopic treatment of lymphoceles resulting from renal transplant (2).

The authors suggest that drainage without suction (with Penrose drain) could be better than tubular drains. This is the subjective impression of some surgeons, but this has to be proved.

Some authors have published good results without drainage after open or robotic radical prostatectomy (3,4). They argue that the routine placement of a pelvic drain may not be required. This is an interesting issue to be investigated.

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T2-Weighted Endorectal Magnetic Resonance Imaging of Prostate Cancer after External Beam Radiation Therapy

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ABSTRACT

Purpose: To retrospectively determine the accuracy of T2-weighted endorectal MR imaging in the detection of prostate cancer after external beam radiation therapy and to investigate the relationship between imaging accuracy and time since therapy.

Materials and Methods: Institutional review board approval was obtained and the study was HIPPA compliant. We identified 59 patients who underwent 1.5 Tesla endorectal MR imaging of the prostate between 1999 and 2006 after definitive external beam radiation therapy for biopsy-proven prostate cancer. Two readers recorded the presence or absence of tumor on T2-weighted images. Logistic regression and Fisher's exact tests for 2x2 tables were used to determine the accuracy of imaging and investigate if accuracy differed between those imaged within 3 years of therapy (n = 25) and those imaged more than 3 years after therapy (n = 34). Transrectal biopsy was used as the standard of reference for the presence or absence of recurrent cancer.

Results: Thirty-four of 59 patients (58%) had recurrent prostate cancer detected on biopsy. The overall accuracy of T2-weighted MR imaging in the detection cancer after external beam radiation therapy was 63% (37/59) for reader 1 and 71% for reader 2 (42/59). For both readers, logistic regression showed no difference in accuracy between those imaged within 3 years of therapy and those imaged more than 3 years after therapy (p = 0.86 for reader 1 and 0.44 for reader 2).

Conclusion: T2-weighted endorectal MR imaging has low accuracy in the detection of prostate cancer after external beam radiation therapy, irrespective of the time since therapy.

Key words: *prostate cancer; radiotherapy; follow-up studies; magnetic resonance imaging*

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INTRODUCTION

Approximately 30% of patients with newly diagnosed prostate cancer undergo external beam radiation therapy (EBRT) as their initial definitive treatment (1). Up to 50% of these patients develop biochemical failure (rising serum prostatic-specific antigen [PSA] after a nadir level has been reached) within 5 years, depending on pre-treatment risk factors (2,3). Biochemical failure may be due to local or systemic recurrence or both (3). Irrespective of the PSA trend, identification of tumor in the treated gland early after completion of radiation therapy is important, because the presence of tumor at needle biopsy performed 2-3 years after radiation, even in patients without clinical or biochemical recurrence, is an important predictor of long-term outcome (4,5). However, a non-invasive alternative to transrectal

biopsy would clearly be preferable for post-radiation monitoring. Over the last decade, MR imaging has emerged as a powerful tool for locoregional evaluation of prostate cancer. The use of MR imaging after radiation therapy is controversial because post-radiation changes such as prostatic atrophy, the development of diffuse low T2 signal intensity, and indistinctness of the normal zonal anatomy might adversely impact the accuracy of T2-weighted MR imaging (6-8). To our knowledge, only five other studies that in total enrolled just 146 patients have previously investigated the method in this same setting, with inconsistent results that range from low to moderate accuracy (9-13). The existing literature has not systematically reported the influence of time since therapy on the accuracy of MR imaging, although there are good reasons to believe this might be an important variable. For example, it is likely that post-radiation MR changes are at least in part reversible. Pickett et al. showed that 26 months or more after EBRT, 60% of patients present with areas of the prostate that have normal metabolism on serial MR spectroscopic imaging (14). It is conceivable that the diverging results reported by prior studies are influenced by the time interval since radiation. Therefore, we undertook this study to retrospectively determine the accuracy of T2-weighted endorectal MR imaging in the detection of prostate cancer after external beam radiation therapy, and to investigate the relationship between imaging accuracy and time since therapy.

MATERIAL AND METHODS

Patients

This was a retrospective single institution study approved by our Committee on Human Research with waiver of informed consent. The study was compliant with requirements of the Health Insurance Portability and Accountability Act. We retrospectively identified, through a cross-correlated computerized search of our medical and radiology information systems, all patients who met the following inclusion criteria:

1 - Definitive treatment of biopsy-proven prostate cancer with external beam radiation therapy with or without associated neoadjuvant/adjuvant androgen deprivation therapy.
2 - Post-treatment 1.5 Tesla endorectal MR imaging of the prostate performed between January 1999 and December 2006.
3 - Post-treatment transrectal ultrasound-guided biopsy of the prostate performed within 180 days of MR imaging.
4 - No additional treatment for prostate cancer.

Fifty-nine patients fulfilled these criteria. The information was redacted for bind review. Eleven of these men were included in a prior preliminary study investigating the use of MR imaging and MR spectroscopic imaging for detection of tumor after radiation therapy (9).

The study group consisted of 59 men with a mean age of 68.8 years (range, 45.2 to 81.6), a mean pretreatment serum PSA level of 18.2 ng/mL (range, 3.5 to 93.0), and the following pretreatment clinical stage (American Joint Committee on Cancer) established on digital rectal examination: T1 (n = 9/59, 15.3%), T2 (n = 31/59, 52.5%), T3 (n = 14/59, 23.7%), or unknown (n = 5/59, 8.5%). The median Gleason score was 7 (range, 5 to 9). The D'Amico risk stratification was based on the clinical stage, PSA level, and Gleason score (15). Patients were categorized as having low risk (n = 7/59, 11.9%), intermediate risk (n = 26/59, 44.1%), or high risk (n = 26/59, 44.1%) tumor.

Forty-two patients received a mean dose of 74.6 Gy (range, 65-82 Gy); the dose administered to 17 patients treated at outside institutions was unknown, but all completed a full course of standard radiotherapy. Seventeen patients (17/59, 28.9%), 5 (5/59, 8.5%), and 6 (6/59, 10.2%) patients underwent neoadjuvant, adjuvant, or neoadjuvant plus adjuvant hormonal therapy for a mean duration of 3.9 months (range, 2 to 5), 8.6 months (range, 5 to 12), and 13.3 months (range, 4 to 21), respectively.

The mean interval from external beam radiation therapy to MR imaging was 44 months (range, 17-138 months), The mean interval between MR imaging and biopsy was 60 days (range, 0-175 days) and most procedures were performed within 90 days of imaging (78%, 46/59).

Patients underwent MR imaging to assess suspected local recurrence on the basis of rising PSA.

At the time of imaging, twenty-two patients (22/59, 37.3%) had biochemical failure, defined as nadir + 2 ng/mL (16). All patients were biochemically disease free following EBRT.

MR Imaging Technique

Patients were scanned in a supine position using the body coil for excitation and a pelvic phased array coil (GE Medical Systems, Milwaukee, WI) in combination with a balloon-covered expandable endorectal coil (Medrad, Pittsburgh, PA) for signal reception on a 1.5-Tesla whole body MR scanner (Signa; GE Medical Systems, Milwaukee, WI). The following parameters were used for acquisition of T1-weighted spin-echo MR images of the pelvis: TR/TE 766/8, slice thickness = 5 mm, interslice gap = 1.5 mm, field of view = 24 cm, matrix 256 x 192, anteroposterior frequency encoding, and 1 excitation. Thin-section high nominal spatial resolution axial and coronal T2-weighted fast spin-echo images of the prostate and seminal vesicles were acquired with the following parameters: TR/effective TE 5000/96 ms, echo train length = 16, slice thickness = 3 mm, interslice gap = 0 mm, field of view = 14 cm, matrix 256 x 192, anteroposterior frequency encoding (to prevent obscuration of the prostate by endorectal coil motion artifact), and 3 excitations.

Imaging Interpretation

Two radiologists, with experience in genitourinary radiology, independently reviewed all the images. The radiologists knew patients were treated with external beam radiation therapy for prostate cancer and that all patients had rising PSA values, but had no access to any other clinical or histological information. Images were reviewed at a picture archiving and communication system workstation (Impax; Agfa, Mortsel, Belgium). The following MR imaging data was recorded:

- Presence or absence of post-biopsy hemorrhage on T1-weighted images. Post-biopsy hemorrhage has low signal intensity on T2-weighted images and can be indistinguishable from cancer. On T1-weighted images, however, these foci present high signal intensity and can thereby be differentiated from suspicious areas of low signal intensity on T2-weighted images that represent cancer, therefore improving the specificity of tumor nodule detection.
- Presence or absence of dominant tumoral lesion on T2-weighted images. A study was considered positive if a focal mass-like nodule or crescentic subcapsular focus of low T2 signal intensity was identified within the hemi-prostate (i.e., the left or right side of the gland) (Figures-1 and 2). Because of the known limitations of tumor localization and registration based on sextant biopsy results (17,18), we localized tumor to the hemi-prostate. The limitation of the prostatic sextant as a unit of analysis is illustrated in a prior study of tumor localization with MR imaging and MR spectroscopic imaging, in which the accuracy of imaging for sextant localization was only 67% (157 of 234) to 74% (173 of 234), but that of imaging for tumor lateralization was 75% (80 of 106) to 88% (93 of 106) (19). The difference was, presumably, at least partially due to errors in registration between imaged sections and biopsy specimens. Such errors are likely to be magnified in the irradiated gland because of radiation-induced shrinkage and distortion of tissue.

We opted to describe only the dominant lesion in each patient based on the results of a study by Pucar et al. that demonstrated that clinically significant local recurrence following radiation therapy presents as a single focus at the site of primary tumor (20).

Standard of Reference

Transrectal ultrasound-guided biopsy was the standard of reference in this study. All but two biopsies were performed at our institution using prostatic nerve blockade. The usual number of specimens that were obtained is 16, using a systematic approach that targeted the right and left sides of the gland at different levels, as well as suspicious areas seen on ultrasound. We retrospectively reviewed the histopathological reports of all procedures. A report was issued by one of the attending pathologists in our institution for all cases, including the two performed at an outside institution. Samples processed at our institution were fixed in formalin immediately after biopsy and subsequently placed in a block of paraffin wax. Microtome sections were then mounted on a glass slide and stained with hematoxylin and eosin. High molecular weight keratin immunoperoxidase staining was also performed on areas suspicious for adenocarcinoma.

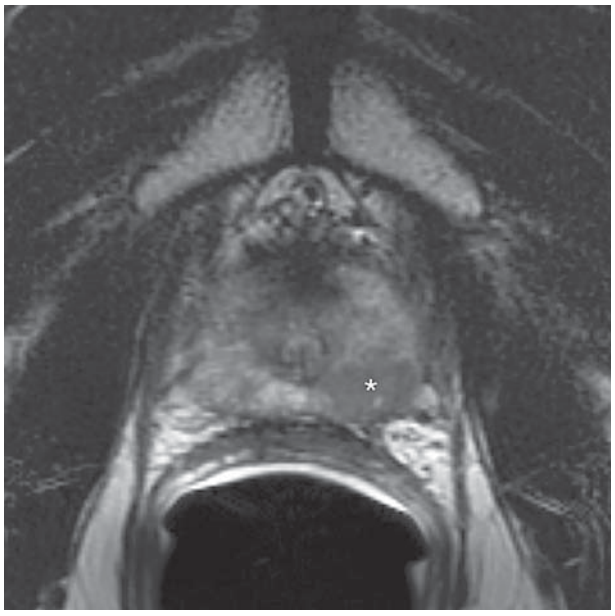

Figure 1 *– 61 year-old man with biopsy-proven recurrence of prostate cancer in the left apex and mid-gland 5 years and 6 months after treatment. Axial T2-weighted image (TE/TR 5000/96) shows a focal nodule of low signal intensity in peripheral zone of the left apex of the prostate (asterisk). Both readers interpreted it as a dominant tumoral lesion in left hemi-prostate.*

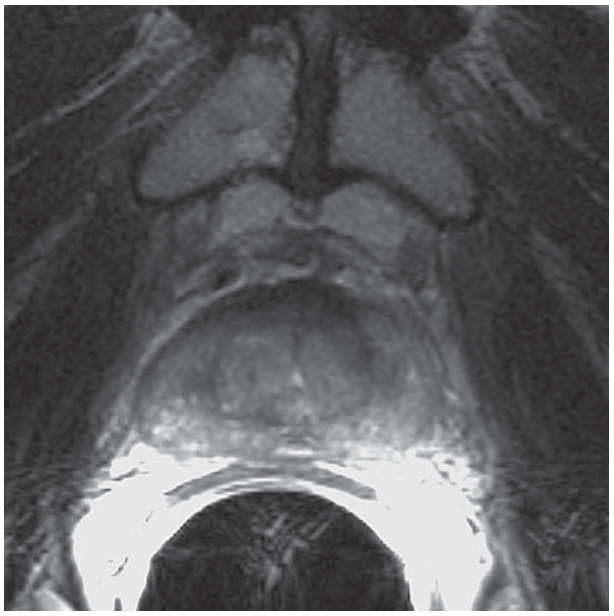

Figure 2 *– 63 year-old man with biopsy-proven recurrence of prostate cancer in the right mid-gland and base 4 years and 2 months after treatment. Axial T2-weighted image (TE/TR 5000/96) shows diffuse low signal intensity in the peripheral zone and central gland. Both readers interpreted it as a negative case.*

Histopathological evidence of post-treatment effect only was considered a negative result (21).

The presence of cancer on histopathology reports was recorded on a per-sextant basis; however, for the reasons stated above, we determined recurrent cancer to be absent or present in the hemi-prostate.

Statistical Analysis

When reading T2-weighted images, our study design called for each reader to only identify the dominant side of a lesion whenever it was bilateral (as explained previously within "Imaging Interpretation"). Therefore, there was an inherent a priori constraint to the data format that cancer could not be identified bilaterally. When analyzing whether readers correctly diagnosed cancer, the definition of the dominant side was taken into account according to the design given in Table-1. That is, a positive diagnosis was considered correct if the reader a) correctly diagnosed the patient as having cancer and if so; b) correctly

Table 1 *– Definition of outcome categories. A positive diagnosis was considered correct if the reader correctly identified tumor and correctly noted the side of the prostate gland containing cancer. In patients in which tumor was bilateral, the reader was considered correct regardless of which side was indicated as dominant.*

		True Positive				True Negative	False Positive				False Negative		
MRI	Right	+	+	-	-	-	+	+	-	-	-	-	-
	Left	-	-	+	+	-	-	-	+	+	-	-	-
Biopsy	Right	+	+	+	-	-	-	-	-	+	+	+	-
	Left	+	-	+	+	-	-	+	-	-	+	-	+

MRI = magnetic resonance imaging.

determined the side of the prostate gland containing cancer - if the cancer was bilateral then the reader was considered correct regardless of which side was named dominant. This allowed us to employ simple and robust non-parametric statistical methods while also taking into account whether the correct side of the prostate was diagnosed as containing cancer.

Kappa statistics were used to determine the level of interobserver agreement.

For the purpose of statistical analysis, the patients in this study were divided in two groups, "early" and "late". Patients who had imaging performed within the first 3 years after external beam radiation therapy formed the group called "early". Conversely, the group named "late" included all patients who were imaged three or more years after treatment. This division was based on the results of the studies by Pollack and Vance (4,5), which suggest that identification of cancer in the first two or three years after treatment negatively impacts long-term outcome. Twenty-five patients were imaged within 3 years of treatment and 34 more in the 3 years after therapy.

Because other factors may have inflenced the accuracy of MR imaging, we assessed the similarity in distribution of several variables between these two groups. The Wilcoxon signed rank test was used to assess their distribution with respect to the continuous variables of pre-treatment PSA level, Gleason score, and radiation dose. Gleason score was treated as a continuous variable because of the large number of possible categories and its ordinal quality. Fisher's exact test was used to assess the distribution of patients within the two groups according to the discrete variables D'Amico risk stratification (15), TNM stage, presence or absence of biochemical failure, and the use of neoadjuvant or adjuvant hormonal therapy. The Freeman-Halton extension of Fisher's exact test was used for contingency tables larger than 2x2.

Logistic regression was used to test for a difference in the accuracy of T2-weighted MR imaging for the detection of cancer in these two groups. The logistic regression model included group ("early" or "late") and diagnosis (presence or absence of cancer on biopsy). The primary test was used for an interaction between group and diagnosis. A significant interaction would indicate a difference in predictive accuracy depending on whether patients were imaged early or late. The model was applied separately to each reader's data.

***Table 2** – Patients' characteristics within groups "early" and "late".*

	Group "Early"	**Group "Late"**	**p Value**
Pre-treatment PSA*	13.9 ng/mL (9.43)	21.85 ng/mL (26.32)	0.83
T stage$^{\Psi}$			0.69
1c	4/22 (18%)	5/32 (16%)	
2a-c	11/22 (50%)	20/32 (63%)	
3a-b	7/22 (32%)	7/32 (22%)	
Gleason score*	6.6 (0.58)	6.73 (1.04)	0.76
median (range)	3+4 (3+3 to 4+3)	3+4 (2+3 to 5+4)	
D'Amico's risk group$^{\Psi}$			0.33
high	10/25 (40%)	16/34 (47%)	
intermediate	10/25 (40%)	16/34 (47%)	
low	5/25 (20%)	2 (6%)	
Radiation dose*	75.5 Gy (3.27)	74.3 Gy (3.73)	0.31
Hormonal therapy$^{\Psi}$	13/25 (52%)	15/34 (44%)	0.60
Biochemical failure$^{\Psi}$	7/25 (28%)	15/34 (44%)	0.28

** = mean (standard deviation), $^{\Psi}$ = n (percentage).*

Table 3 *– Summary of overall diagnostic accuracy.*

	Reference			Results				Diagnostic Accuracy					
	N	Pos	Neg	TP	FN	FP	TN	Se (95% CI)	Sp (95% CI)	PPV (95% CI)	NPV (95% CI)	+LR (95% CI)	-LR (95% CI)
Reader 1	59	34	25	21	13	9	16	0.62 (0.45-0.76)	0.64 (0.45-0.80)	0.7 (0.52-0.83)	0.55 (0.38-0.72)	1.72 (0.96-3.08)	0.6 (0.36-1.0)
Reader 2	59	34	25	23	8	9	19	0.74 (0.57-0.86)	0.68 (0.49-0.82)	0.72 (0.55-0.84)	0.7 (0.52-0.84)	2.31 (1.3-4.11)	0.38 (0.2-0.73)

N = sample size; Pos = positive; Neg = negative; TP = true-positive; FN = false-negative; FP = false-positive; TN = true-negative; Se = sensitivity; Sp = specificity; PPV = positive predictive value; NPV = negative predictive value; +LR = likelihood ratio of a positive result; -LR = likelihood ratio of a negative result.

Table 4 *– Results of the diagnostic accuracy of MR imaging by group.*

	Early Group (less than 3 years) Standard of Reference: positive = 9, negative = 16						Late Group (more than 3 years) Standard of Reference: positive = 25, negative = 9					
	Sensitivity	Specificity	PPV	NPV	+LR	-LR	Sensitivity	Specificity	PPV	NPV	+LR	-LR
Reader 1	56 (27-81)	69 (44-86)	50 (24-76)	73 (48-89)	1.78 (0.7-4.52)	0.65 (0.29-1.44)	64 (45-80)	56 (27-81)	80 (58-92)	36 (16-61)	1.44 (0.66-3.17)	0.65 (0.30-1.42)
Reader 2	63 (31-86)	82 (59-94)	63 (31-86)	82 (59-94)	3.54 (1.11-11.28)	0.46 (0.18-1.14)	78 (58-90)	46 (21-72)	75 (55-88)	50 (24-76)	1.44 (0.8-2.57)	0.48 (0.17-1.31)

PPV = positive predictive value; NPV = negative predictive value; +LR = likelihood ratio of a positive result; -LR = likelihood ratio of a negative result; parenthesis = 95% confidence interval.

Statistical calculations were performed using SAS/STAT® software v9.1 (SAS Institute Inc., Cary, NC).

RESULTS

Histopathological Findings

Forty-one hemi prostates (41/118, 34.7%) in thirty-four patients (34/59, 57.6%) had evidence of cancer on histopathological analysis of transrectal ultrasound-guided biopsy samples. Nineteen patients had recurrence in the right side of the prostate, 8 in the left, and 7 bilaterally. Nine of these patients were part of early post-treatment group (9/25, 36%) and 25 were part of the late post-treatment group (25/34, 73.5%). All seven patients with tumor detected on both sides of the prostate were part of the latter group.

Patient Characteristics

There were no statistically significant differences in the balance of patients within groups "early" and "late" according to pre-treatment PSA, clinical stage, Gleason score, D'Amico's risk stratification, radiation dose, neoadjuvant and/or adjuvant hormonal therapy, and evidence of biochemical failure at the time of imaging (Table-2).

MR Imaging Results

None of the readers detected intra-prostatic hemorrhage on T1-weighted MR images of 13 patients (13/59, 22.0%) who underwent biopsy prior to imaging.

Overall, the diagnostic accuracy of T2-weighted MR imaging after external beam radiation therapy was 63% (37/59), for reader 1, and 71% (42/59), for reader 2. The sensitivity and specificity of the method was 62% (21/34) and 64% (16/25), for reader 1, and 74% (23/31) and 68% (19/28), for reader 2, respectively. These results, along with the predictive values and likelihood ratios, are detailed in Table-3.

The interobserver agreement was considered good on a per-patient and per-hemi-prostate basis (Kappa coefficient value = 0.59 and 0.69, respectively).

The results of the diagnostic accuracy of MR imaging per group, i.e. "early" and "late", are summarized in Table-4. For both readers, logistic regression failed to demonstrate a statistically significant difference in the ability of T2-weighted MR imaging to detect cancer based on whether patients were imaged before or after 3 years (reader 1, $p = 0.86$; reader 2, $p = 0.44$).

DISCUSSION

Despite our rather liberal criteria for a true positive outcome - identifying tumor within a hemi-prostate, even if tumor was bilateral - the results of our study suggest that T2-weighted endorectal MR imaging has low accuracy for the detection of recurrent disease in patients who have undergone definitive treatment with external beam radiation for prostate cancer. The few published studies on MR imaging after EBRT have suggested T2-weighted MR imaging has low to moderate accuracy for the detection of tumor after radiation treatment (9-13). The variability in the numbers reported by the different authors is mostly dependent on three factors: prevalence of disease in the sample, sample size, and statistical analysis methodology.

Pucar et al. enrolled only nine patients, all of which had known recurrence following radiation therapy. Using a sextant approach, they found that MR imaging had a sensitivity of 68% and specificity of 96%; however, they did not adjust for clustering effects (10). Sala et al. reported areas under the receiver-operating curve (AU-ROC) of 75% and 61%. They also reported the sensitivity and specificity of MR imaging based on the dichotomization of results measured using a five-point scoring system. These results were very similar to ours (sensitivity = 55-76%, specificity = 65-73%) (12). In a study that enrolled 22 patients, Rouviere et al. reported a sensitivity ranging from 68% to 78% (11). Unfortunately, all but three patients had recurrence, decreasing the significance of the calculation of specificity. Coakley et al. included 21 patients in their study and used the hemi-prostate as unit of analysis. Accounting for clustering effects, they found an AU-ROC of 49% and 51% for MR imaging (9). The study by Haider et al. also had a sample size (n = 49) and results that were similar to ours, considering the 95% confidence intervals. Ac-

cording to their study, MR imaging had a sensitivity and specificity of 58% and 52%, respectively (13).

The results of all above-mentioned studies, including ours, suggest that MR imaging alone is insufficient for the evaluation of such populations of patients and raises the question of whether other imaging modalities should be used, separately or in conjunction with T2-weighted MR imaging. Among the options available, multiparametric endorectal MR imaging - an approach that incorporates other MR techniques, such as MR spectroscopic imaging, dynamic enhanced MR imaging, and diffusion-weighted MR imaging - is promising. Coakley et al. found that a combined approach using MR imaging and MR spectroscopic imaging improved detection of tumor (9). Both Haider and Rouviere reached similar conclusions when they investigated the incremental value of dynamic enhanced MR imaging (11,13). Although these studies support the use of multiparametric MR imaging in patients treated with external beam radiation therapy, the results are preliminary and further investigation with a larger, prospective trial is ultimately required.

As a secondary analysis, we investigated if the accuracy of the MR imaging was influenced by the time interval between radiation treatment and MR imaging. This assumption was based on observation of recovery of the usual zonal anatomy after radiation and/or hormonal therapy and on the results of a study by Pickett et al. (14) that showed recovery of normal metabolism at MR spectroscopic imaging after treatment. We dichotomized the subjects in two groups, those whose MR images were acquired within 3 years after treatment and those whose imaging was performed after 3 years. This decision was supported by the results presented by Pollack and Vance (4,5), which suggest that identification of cancer in the first two or three years after treatment negatively impacts long-term outcome. Our results did not demonstrate an influence of time since treatment on accuracy of MR imaging on a logistic regression model. It is unknown if this in fact represents an accurate picture of the situation or just the result of insufficient power due to a small sample size.

It has been previously demonstrated that hormonal deprivation therapy can significantly reduce tumor volume and decrease peripheral zone signal on T2-weighted images (22), hence having an additional influence in tumor detection on MR imaging. Although it would be interesting to stratify patients in two groups (with and without androgen deprivation therapy) to determine how this would affect our results, it would not possible to obtain any meaningful results of accuracy due to the small number of subjects in each subgroup. This is an issue that must be addressed in future studies.

Our study has limitations. First, it was a retrospective, single institution study. Our results probably are not widely generalizable, as the expertise in MR imaging acquisition and interpretation varies among institutions. Because of our retrospective research design, we probably incurred a sample selection bias, as we included only patients who had a transrectal ultrasound-guided biopsy. It may be expected that the prevalence of recurrent cancer in our population is higher than in the general population of patients treated for prostate cancer with external beam radiation therapy. This could influence our results, as both positive predictive value and negative predictive value are directly related to the prevalence of disease. Although sensitivity and specificity would not be affected. On the other hand, the indications of MR imaging after radiation therapy have not yet been established and more likely the modality will be added to the armamentarium used to investigate patients with suspected local recurrence on the basis of clinical examination or PSA measurements. In fact, our population is representative of this cohort and therefore our results are useful for future standard procedure. Second, our sample size is not large. This has two major effects on our results; it produces a wide 95% confidence interval for diagnostic accuracy estimations and does not provide us sufficient power to reject the null hypothesis - i.e., the interval of time between treatment and MR imaging does not affect the detection of cancer with T2-weighted MR imaging - if this is fact false (type II error). The wide confidence intervals explain the apparent difference of accuracy between the two readers - not statistically significant - despite relatively good interobserver agreement. Third, transrectal ultrasound-guided biopsy is an imperfect standard of reference. The use of an imperfect standard of reference results in bias of the estimated error rates of MR imaging and the direction of this

bias is usually downward (23). In our study, which has a relatively large number of patients with disease, i.e. positive biopsy, this bias is probably less significant for the estimation of sensitivity than specificity. It is important, though, to make clear that our results may overestimate the true accuracy of the modality. In this setting, however, overestimation would in fact provide further support to our conclusion: T2-weighted MR imaging appears to have low accuracy for detection of recurrent cancer in patients who underwent external beam radiation therapy. Although whole-mount histopathologic analysis of salvage prostatectomy specimens may be considered a preferable standard of reference, such surgery is infrequently performed in the population we investigated. In addition, this approach also has limitations. In a retrospective study, for instance, it may result in verification bias, as the decision to proceed to surgery is likely influenced by positive results of MR imaging. Our use of the hemi-prostate rather than the prostate sextant as the unit of analysis might also be criticized, although as noted above sextant localization is inaccurate when biopsy is compared to radical prostatectomy specimens, likely due to errors in sextant localization of ultrasound-guided biopsy needles. Such errors are likely to be even greater in the shrunken post-radiation gland. Lateralization should be less subject to such registration problems.

Lastly, the option to consider the reader correct regardless of which side was named dominant in bilateral tumors can also lead to incorrect higher accuracies of the imaging method. We opted for this approach for two reasons: 1) this allowed us to employ simple and robust non-parametric statistical methods while also taking into account whether the correct side of the prostate was diagnosed as containing cancer; and 2) detection of local recurrence in one side, even if disease is bilateral, provides sufficient information for determining management of these patients, as the current standard is to treat them with salvage brachytherapy or salvage prostatectomy (+/- systemic therapy), techniques that treat the entire gland. Irrespective, overestimation of our results supports our conclusion.

In conclusion, T2-weighted MR imaging appears to have low accuracy for detection of recurrent cancer in patients who underwent external beam radiation therapy. Further and larger studies are necessary to confirm these results and to determine if the interval of time between treatment and MR imaging truly has no effect on the accuracy of the method.

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CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

The detection of locally recurrent prostate cancer, after external radiation therapy (EBRT), is essential since further treatment options are variable. This includes additional irradiation of the prostate, hormonal therapy, salvage prostatectomy and other new treatment options such as cryosurgery and transrectal high-intensity focused ultrasound. Although several treatment options are available, the management of recurrent prostate cancer after EBRT is a difficult task since all these modalities are associated with high risks of complication (1). For these reasons, precise detection of local recurrence of the tumor is of utmost importance for the management of these patients. The authors performed a retrospective study in order to determine the accuracy of T2-weighted endorectal MR imaging in the detection of prostate cancer after EBRT, and also to investigate the relationship between imaging accuracy and time since therapy. They concluded that "T2-weighted endorectal MR imaging has low accuracy in the detection of prostate cancer after external beam radiation therapy, irrespective of the time since therapy".

As pointed out by the authors in the introduction of their manuscript, tumor depiction with conventional endorectal magnetic resonance imaging in the irradiated gland is of limited value due to treatment-related changes that include prostatic shrinkage, diffuse low T2 signal intensity in the gland, and indistinctness of the normal zonal anatomy (2,3). Since irradiated prostate gland usually appears small and diffusely hypointense on T2-weighted images, magnetic resonance spectroscopic imaging (MRSI), which depicts abnormal metabolism rather than abnormal anatomy, has been shown to be much better technique for the detection of local tumor recurrence and for the demonstration of complete metabolic atrophy (4-6). At our institution, in the last 5 years, we have been using a comprehensive protocol for the detection of recurrent disease in patients treated with EBRT. This protocol consists of a combination of conventional endorectal T2-weighted image with multiparametric functional MRI studies (MRSI, dynamic contrast enhanced and diffusion-weighted images). Using the transrectal guided biopsy as reference, similarly to the authors, we have so far found greater accuracy when using this protocol as compared with conventional T2-weighted images (7).

Regarding the influence of time after EBRT, we found that serial MR spectroscopic imaging is also superior to convention endorectal MRI to demonstrate areas of normal or abnormal metabolism, which can be observed several months after the end of EBRT. Further studies, however, are warranted to confirm this hypothesis.

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EDITORIAL COMMENT

Detection of post-treatment recurrence of prostate cancer is a challenging situation, both after radical prostatectomy and radiation therapy, since PSA alone may not differentiate between biochemical, local and/or systemic recurrence.

Endorectal MRI (E-MRI), given its intrinsic high contrast resolution, would be the ideal imaging exam for non-invasive detection of local recurrence. However, T2-weighted images of the prostate (the standard imaging technique for prostate MRI) may not suffice for the detection of recurrence, especially after radiation therapy.

The article from Dr. Westphalen et al. reemphasizes the limitations of T2-weighted MRI for the detection of local recurrence after radiation therapy, regardless of the time interval between the procedure and the imaging study.

It should be kept in mind, however, that these results certainly do not diminish the value of E-MRI for the purpose of local recurrence detection. Recent studies have shown that the use of complimentary MRI techniques (namely, spectroscopy and contrast-enhanced dynamic MRI) significantly increases accuracy of the method for the detection of local recurrence, both after radical prostatectomy and after radiation therapy (1,2). Moreover, a recent article correlating MRI and step-section pathology demonstrated that clinically significant local recurrence after radiation therapy occurs at the same site of the primary tumor, so the use of E-MRI before and after treatment could lead to early detection of local recurrence suitable to salvage therapy (3).

Therefore, we can conclude that E-MRI, when used appropriately with the correct dedicated techniques, should be considered in the diagnostic workflow of patients with suspected local recurrence after prostate cancer treatment.

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Risk Factors for Bone Loss with Prostate Cancer in Korean Men Not Receiving Androgen Deprivation Therapy

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ABSTRACT

Purpose: Preexisting bone loss in men with prostate cancer is an important issue due to the accelerated bone loss during androgen deprivation therapy (ADT). In addition, a high prostate-specific antigen (PSA) level has been reported to be related to bone metabolism. This study assessed the factors associated with osteoporosis in Korean men with non-metastatic prostate cancer before undergoing ADT.

Materials and Methods: The study enrolled patients admitted for a prostate biopsy because of a high PSA or palpable nodule on a digital rectal examination. We divided the patients (n = 172) according to the results of the biopsy: group I, non-metastatic prostate cancer (n = 42) and group II, benign prostatic hypertrophy (BPH; n = 130). The lumbar bone mineral density (BMD) was evaluated using quantitative computed tomography. The demographic, health status, lifestyle, body mass index (BMI), serum testosterone concentration, and disease variables in prostate cancer (Gleason score, clinical stage, and PSA) were analyzed prospectively to determine their effect on the BMD.

Results: The estimated mean T-score was higher in group I than in group II (-1.96 ± 3.35 vs. -2.66 ± 3.20), but without statistic significance ($p = 0.235$). The significant factors correlated with BMD in group I were a high serum PSA ($\beta = -0.346$, $p = 0.010$) and low BMI ($\beta = 0.345$, $p = 0.014$) in the multiple linear regression model. Also old age ($r = -0.481$, $p = 0.001$), a high serum PSA ($r = -0.571$, $p < 0.001$), low BMI ($r = 0.598$, $p < 0.001$), and a high Gleason's score ($r = -0.319$, $p = 0.040$) were the factors related to BMD in the correlation. The significant factors correlated with BMD in group II were old age ($\beta = -0.324$, $p = 0.001$) and BMI ($\beta = 0.143$, $p = 0.014$) in the multiple linear regression model.

Conclusions: The risk factors for osteoporosis in men with prostate cancer include a low BMI, and elevated serum PSA. Monitoring BMD from the outset of ADT is a logical first step in the clinical strategy to avoid or minimize potential bone-related complications in these patients.

Key words: *prostate neoplasm; osteoporosis; androgen deprivation therapy; prostate specific antigen*
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INTRODUCTION

In men, 36% of osteoporosis is due to low androgen levels, which can occur with congenital hypogonadism, the aging process, or androgen deprivation therapy (ADT) for the treatment of advanced prostate cancer (1). Bone is the most common site of metastasis in many types of cancer, including advanced prostate cancer. Several studies have reported that ADT can induce bone loss and increase bone fracture risk in men with prostate cancer (2-4). Moreover, many other authors have reported that patients with prostate cancer had previously developed osteoporosis before ADT compared to non-prostate cancer patients (5). This suggests that factors beside ADT may cause osteoporosis in prostate cancer, but

no data on this subject has been reported for Korean patients with prostate cancer.

Recently, the increased life expectancy, advanced diagnostic techniques, and Westernized eating habits have contributed to a high incidence of prostate cancer in Koreans and an increased mortality rate due to co-morbidity. Thus, predicting and preventing the progression of osteoporosis in patients with prostate cancer is of critical importance. Before initiating ADT, it is necessary to identify the causes of bone loss and related risk factors for osteoporosis. However, who should undergo bone mineral density (BMD) testing before ADT remains unclear. There is a major need to determine ways to treat patients with prostate cancer undergoing ADT without increasing the risk of osteoporosis. This study evaluated the factors associated with osteoporosis in patients with non-metastatic prostate cancer before undergoing ADT as compared to those with benign prostate hypertrophy (BPH) alone.

MATERIALS AND METHODS

After informed consent was obtained from all patients, a prospective trial was initiated at Chonnam National University Hospital from January to December 2005. This study enrolled patients hospitalized for a prostate biopsy because of a high PSA or palpable nodule on rectal examination. Based on previous medical history and physical examination, patients with thyroid or parathyroid disease, uncontrolled diabetes mellitus, cardiovascular disease, digestive disorders, and chronic steroid users were excluded, as well as patients found to have bone metastasis on plain film X-rays and a bone scan. Patient information on demographics, health status, lifestyle, tobacco use, and body mass index (BMI) were obtained. The patients were divided into two groups according to the result of the prostate biopsy: group I, patients with prostate cancer (n = 42), and group II, patients with BPH (n = 130). The general conditions of the patients assessed according to performance status were good and they reported light physical activity and moderate intakes of calcium, alcohol, and caffeine. We evaluated the relationship between the patient characteristics and disease variables. This was analyzed prospectively using univariate and multivariate methods to determine their role in the BMD levels previously established using quantitative computed tomography (QCT) of the lumbar spine. The Institutional Review Board at our hospital approved the study.

Prostate Cancer Disease Variables

The patients' charts were reviewed to obtain information on clinical variables pertaining to prostate cancer: clinical stage, Gleason score, and PSA. To measure PSA (Access Assay, Hybritech) and total testosterone (Immunoenzymatic assay, Beckman), serum was obtained at between 08:00 and 09:00 h.

Bone Mineral Density

The BMD in L1-4 was measured using QCT. Using the World Health Organization Criteria, a normal BMD was defined as one greater than -1 standard deviation (SD) below the young adult mean value (T-score), osteopenia as a T-score between -1 and -2.5 SDs, and osteoporosis as a T-score of -2.5 or less (6).

Statistical Analysis

Descriptive, comparative, univariate, and multivariate analyses using the Statistical software package for the Social Sciences, version 12.0 (SPSS Inc., Chicago, IL) were performed to describe BMD and the associations between it and the disease variables. Simple correlation analysis was performed using the nonparametric Spearman correlation coefficient. An independent samples t-test was used for comparison analysis. Variables statistically significant in the univariate analysis were included in the multiple linear regression model with BMD of the lumbar spine as the dependent variable. Two-tailed tests were used for all correlation and comparison analyses. P values of 0.05 or less were considered statistically significant.

RESULTS

No differences were observed in the basic health characteristics between the two age-matched groups (over 65 years old), except for PSA, as summarized in Table-1. Most of the patients were sedentary

Table 1 – *A comparison of the disease variables between the two groups.*

	Mean ± SD		T	p Value
	Group I (n = 42)	Group II (n = 130)		
Age (years)	71.48 ± 6.80	70.75 ± 6.10	-0.648	0.518
Serum PSA (ng/mL)	17.12 ± 14.93	9.65 ± 9.61	-3.042	0.004
BMI (kg/m^2)	23.80 ± 2.94	22.98 ± 2.60	-1.724	0.087
s-Testosterone (ng/mL)	3.14 ± 1.42	3.30 ± 1.66	-1.822	0.061
BMD, T-score (mean ± SD)	-2.66 ± 3.20	-1.96 ± 3.35	1.193	0.235
Smoking (%)	22.69	21.42	3.345	0.601

Group I = prostate cancer group; Group II = benign prostate hyperplasia group; PSA = prostate specific antigen; BMI = body mass index; BMD = bone mineral density; Dependent variables = T-score.

and did not engage in physically demanding sports or recreational activity, but only in light exercise, such as short walks. Among the former and current smokers, the pack years ranged from 5 to 62. Additional information on the prostate cancer disease variables for group I is summarized in Table-2.

The BMD between the Two Groups

No significant difference was detected in the prevalence of bone loss between the two groups. In group I, 69.05% had osteopenia (16.67%) or osteoporosis (52.38%) of the spine, while in group II, 55.38% had osteopenia (9.23%) or osteoporosis (46.15%). The estimated mean T-score was higher in group I than in group II (-1.96 ± 3.35 vs. -2.66 ± 3.20), but the difference was not statistically significant (p = 0.235) (Table-1). For all of the participants in this study, old age (r = -0.371, p < 0.001), a high PSA (r = -0.209, p = 0.006), and low BMI (r = 0.226, p = 0.003) were significantly correlated with bone loss.

Table 2 – *Basic characteristics of group I (prostate cancer group).*

Characteristics	N (%)
Prostate cancer stage	
cT1NxM0	18 (42.8)
cT2NxM0	22 (25.4)
cT3NxM0	2 (4.8)
Gleason's score	
3+3=6	4 (9.5)
7 (4+3, 3+4)	16 (38.1)
4+4=8	12 (28.6)
9 (4+5, 5+4)	10 (28.9)

The BMD in Patients in Group-I

The mean patient age was 71.48 years. The number (%) of participants by clinical stage T1, T2, and T3 was 18 (42.8), 22 (25.4), and 2 (4.8) respectively and by a Gleason's score of 6, 7, 8, and 9 was 4 (9.5), 16 (38.1), 12 (28.6), and 10 (28.9), respectively. Of those with prostate cancer, 69.05% had osteopenia (16.67%) or osteoporosis (52.38%) of the spine (mean T-score -2.66 ± 3.20). The significant factors correlated with BMD in group I were a high serum PSA (β = -0.346, p = 0.010) and low BMI (β = 0.345, p = 0.014) in the multiple linear regression model (Table-3). Also an old age (r = -0.481, p = 0.001), a high serum PSA (r = -0.571, p < 0.001), low BMI (r = 0.598, p < 0.001), and a high Gleason's score (r = -0.319, p = 0.040) were the factors related with BMD in the univariate analysis (Table-4).

The BMD in Patients in Group-II

The mean patient age was 70.7 years. Of those with BPH, 55.38% had osteopenia (9.23%) or osteoporosis (46.15%) of the spine (mean T-score -1.96 ± 3.35). The significant factors correlated with BMD in group II were old age (β = -0.324, p = 0.001) and BMI (β = 0.143, p = 0.014). Smoking, serum testosterone and clinical stage were not significantly correlated with BMD (Table-5).

Table 3 – *The factor associated with bone loss in Group I (prostate cancer).*

	Standardized Coefficients	**T**	**p Value***
	Beta		
Age (years)	-0.228	-1.797	0.081
Smoking (%)	-0.040	-0.334	0.741
Serum PSA (ng/mL)	-0.346	-2.729	0.010
BMI (kg/m^2)	0.345	2.587	0.014
Serum Testosterone (ng/mL)	0.095	0.711	0.482
Clinical stage	0.032	0.269	0.790
Gleason's score	-0.120	-0.991	0.328

*Adjusted R^2 = 0.479; Dependent variables = T-score; * calculated from multiple linear regression model.*

Table 4 – *The factors associated with bone loss in Group I (prostate cancer group).*

	T-score	**Age** (years)	**Smoking** (%)	**s-PSA** (ng/mL)	**BMI** (kg/m^2)	**s-Testosterone** (ng/mL)	**Clinical Stage**
Age (years)	-0.481**						
Smoking (%)	0.033	-0.155					
s-PSA (ng/mL)	-0.571**	0.296	-0.143				
BMI (kg/m^2)	0.598**	-0.355*	-0.081	-0.391*			
s-Testosterone (ng/mL)	0.114	-0.086	-0.215	0.035	0.027		
Clinical stage	0.157	-0.154	-0.175	-0.034	0.238	0.080	
Gleason's score	-0.319*	0.244	-0.171	0.223	-0.221	-0.364*	0.092

***p < 0.01; *p < 0.05; calculated from Spearman's correlation analysis; Dependent variables = T-score.*

Table 5 – *The factors associated with bone loss in Group II (benign prostatic hyperplasia group.*

	Standardized Coefficients	**T**	**p Value***
	Beta		
Age (years)	-0.324	-4.216	0.001
Serum PSA (ng/mL)	-0.035	-0.475	0.635
BMI (kg/m^2)	0.143	1.794	0.014
Smoking	0.113	1.496	0.075
Serum Testosterone (ng/mL)	0.021	0.274	0.784

*Adjusted R^2 = 0.118; dependent variables = T-score; * calculated from multiple linear regression model.*

COMMENTS

As the prevalence of prostate cancer and osteoporosis increases with age, many patients may already have osteoporosis when diagnosed with prostate cancer. Orchiectomy and the administration of a gonadotropin-releasing hormone agonist, which is the main treatment for metastatic prostate cancer,

have been reported to cause significant bone loss and lead to bone fracture (7). This is of great concern for men with prostate cancer who will receive ADT (8). Therefore, osteoporosis should be prevented in men with prostate cancer who may require ADT.

Prostate cancer produces and secretes abundant PSA, which is not synthesized in other tumors or tissues. PSA is an important, widely used serologic marker for prostate cancer, but its role in bone metastases is still unclear. PSA, a serine protease, and matrix metalloproteinases are involved in the breakdown of the extracellular matrix that promotes the invasion and metastasis of tumor cells in bone (9). In addition, elevated serum PSA levels are associated with advanced prostate cancer, and prostate cancer cells stimulate the release of various cytokines, which activate osteoclasts and bone resorption (10). Prostate cancer preferably metastasizes to bone and produces primarily osteoblastic phenotypes, unlike other cancers, which are associated with osteoclast formation. Among the known osteogenic factors produced by prostate cells, bone morphogenic proteins, endothelin-1, insulin-like growth factors, parathyroid hormone-related peptide, transforming growth factor-β, and PSA, the latter is uniquely produced by prostate cancer cells (11-16). Men with prostate cancer with poorly differentiated cells and a high Gleason's score have lower testosterone levels than those with well differentiated cells and a low Gleason's score (17). Generally, poorly differentiated prostate cancer is very progressive and metastasizes rapidly; the clinical stage is already high at diagnosis.

Although aging and a low BMI are known risk factors for osteoporosis, whether the serum PSA level or Gleason's score are risk factors for osteoporosis remains unclear in men with prostate cancer. In this study sample, a low BMI and elevated serum PSA levels were significant factors of decreased BMD in the multivariate analysis. Also, old age, a low BMI, elevated serum PSA levels, and a high Gleason's score were significantly associated with bone loss in men with prostate cancer, in the univariate analysis. These results suggest that men with prostate cancer, who are slender and have higher serum PSA levels, are at increased risk of developing a decreased BMD after ADT. In this study, the total serum testosterone was not different between the two groups and was not significantly correlated with BMD. In addition, no correlation with bone loss was observed with the clinical stage of the disease. Although smoking causes osteoporosis, no correlation with bone loss was detected in our study sample, differing somewhat from our previous prediction. This may have been caused by the relatively small number of patients in this study sample.

To date, no convincing study on the status of BMD in non-metastatic prostate cancer prior to ADT had been conducted in Korea. In the present study, 69.05% of the patients with non-metastatic prostate cancer had osteopenia (16.67%) or osteoporosis (52.38%) of the spine before ADT, which is similar to another study in which 73.5% had osteopenia (55.9%) or osteoporosis (17.6%) of the spine (8).

One of the limitations of this study is that the exact intake of calcium and vitamin D, as well as smoking status and the type of daily activities, which are other factors potentially affecting BMD, were not considered. For accuracy, a future study must include all of these factors. In addition, the small size of the non-metastatic prostate cancer group in this study is a limitation. Many studies have recommended that one should check the baseline BMD in all men before starting ADT when osteoporotic risk factors are found (18,19). One should also consider performing BMD studies in older men who have a high serum PSA and a slender stature before initiating ADT in prostate cancer.

CONCLUSIONS

The risk factors for osteoporosis in men with prostate cancer include old age, a low BMI, and elevated serum PSA. Consideration should be given to performing BMD studies in these men before initiating ADT in prostate cancer. Monitoring BMD from the outset of ADT is a logical first step in the clinical strategy to avoid or minimize potential bone-related complications in these patients.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

This is an interesting paper describing risk factors for osteopenia in men with prostate cancer and benign prostatic hyperplasia undergoing androgen deprivation therapy (ADT). The work describes high prostate specific antigen and low body mass index as risk factors for men with prostate cancer about to undergo ADT. It is important to screen such men prior to ADT to determine if further steps are needed, such as vitamin D and calcium supplementation or bisphosphonate treatment.

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Sperm Banking for Male Cancer Patients: Social and Semen Profiles

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ABSTRACT

Purpose: Report the characteristics of cryopreserved semen from a cohort of male cancer patients, attitudes towards cryopreservation and outcomes of semen samples based on a 12-year cryopreservation program.
Material and Methods: Data from 98 male cancer patients whose sperm samples were banked were evaluated. Demographic parameters, semen characteristics, destination of sperm banked samples and questionnaires answered by the patients regarding cryopreservation time were evaluated.
Results: The cancer diagnoses were testicle (56.1%), prostate (15.3%), Hodgkin's lymphomas (9.2%), non-Hodgkin's lymphomas (7.1%), leukemia (3.1%) and other malignancies (9.2%). The patients with testicular cancer presented lower sperm concentration ($p < 0.001$); however, there were no differences with the percentage of normozoospermic patients among cancer type groups ($p = 0.185$). A shorter time between cancer diagnosis and sperm banking was observed for testicular and prostate cancer patients ($p < 0.001$). Most of the patients (89.5%) favored sperm banking as a fertility preservation method.
Conclusions: Although less than 20% of banked sperm samples were disposed of, the majority of patients related sperm banking with safe for fertility preservation. Our results show that all male cancer patients of reproductive age facing cancer treatment could be offered sperm banking.

Key words: *cancer; fertility; semen; sperm banks*
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INTRODUCTION

Cancer is the leading cause of death in the world, accounting for 7.6 million mortality cases in 2005. Cancer treatments (surgery, radiotherapy and chemotherapy) are undertaken to remove malignancies, prolong the patient's life and improve their quality of life. Some types of cancer have higher cure rates than others. When detected early and treated according to best practices, one-third of cancer cases can be cured (1).

The cure rate of malignancies among patients with testicular cancer, Hodgkin's disease, lymphoma, or leukemia can be as high as 90%. However, depending on the underlying disease, age, type and dose of therapeutic agent used, and duration of treatment, these patients might present a post-therapy reproductive dysfunction, with 15-30% remaining sterile in the long term (2-4). With approximately 15% of male cancer patients at less than 55 years of age when first diagnosed (5), the impairment of fertility among surviving young cancer patients who

have not yet started a family has gained increasing clinical importance.

Cytostatic chemotherapy targets cells outside the G0 phase mainly destroy the rapidly proliferating spermatogonias. It is often following such treatments that the majority of male cancer patients develop azoospermia (2). The time for recovery of spermatogenesis is dose dependent and consequently difficult to predict. It has been reported that, while male cancer patients receiving low doses of cytostatic agents may expect recovery of spermatogenesis around 12 weeks after chemotherapy, permanent azoospermia occur in more than 50% of the patients receiving high doses (6).

High-dose radiotherapy to the pelvic region is another important treatment modality in patients with carcinoma in situ of the testis or cancer of the prostate, rectum and bladder, exposing patients to high risks of developing permanent infertility. The impairment of spermatogenesis after radiotherapy is also site- and dose-dependent (7).

Cancer surgery affecting the genital or pelvic organs can also have adverse consequences for fertility, namely, reduced sperm concentration (following unilateral orchiectomy for testicular cancer) (8), erectile dysfunction (after prostatectomy performed in prostate cancer patients) (9), or dry ejaculation (from radical retroperitoneal lymph-node dissections) (10).

Moreover, important alterations of spermatogenesis can be detected prior to treatment in the majority of young patients with testicular cancer or lymphoma and are thus unrelated to cytotoxic chemotherapy (7). Patients should be made aware of the possibility that up to 15% of male patients will already be azoospermic before they have had any chemotherapy or radiotherapy treatment (11).

Early reports on sperm banking for oncological patients showed that few patients had semen samples compatible with successful cryopreservation employed in intra-uterine insemination (12), and pregnancy rates remained very poor (13). As a result, many oncologists considered semen cryopreservation an ineffective, expensive and time consuming fertility strategy for cancer patients.

However, with the introduction of intracytoplasmic sperm injection (ICSI), surviving male cancer patients may now have a better chance of fathering children who are genetically their own, even with the poorest semen samples (14,15).

Furthermore, recent reports have shown that DNA fragmentation in sperm samples from oncological patients before undergoing surgery, chemotherapy or radiotherapy treatments are comparable to those of infertile male partners in assisted reproduction programs and of men with proven fertility (16,17).

Currently, the sperm banking and the assisted reproduction techniques, before and after the treatment respectively, can be successfully offered to male cancer patients. Ideally, semen cryopreservation should be performed before cancer treatment is started, and, if possible, multiples samples should be preserved. The decision to offer each technique is based on the semen quality pre-freeze and post-thaw. Where adequate amounts of spermatozoa have been banked and semen quality allows, intra-uterine insemination using the thawed spermatozoa could be considered, and in vitro fertilization (IVF) techniques including ICSI are generally recommended where the quantity of sperm available is small or as deemed necessary per female pathology (18).

In this study, our specific aims were examining the pre-freeze semen quality and discussing the social importance of sperm banking to male cancer patients. In particular, we report the characteristics of cryopreserved semen from a cohort of male cancer patients, the patients' attitudes toward semen cryopreservation, and tracking of sperm samples from a 12-year cryopreservation program.

MATERIALS AND METHODS

Between July 1996 and January 2008, 98 male cancer patients were referred to our center for sperm banking before receiving potential gonadotoxic therapy, chemotherapy, and/or radiotherapy. All patients received complete information regarding options for future use of sperm samples and the IVF program.

This study was approved by the Institutional Review Board. Patients gave written informed consent for the study procedures and the use of their clinical and biological data for research purposes.

Patients were asked to collect ejaculated semen samples a minimum of three times, except for those patients who started chemotherapy immediately after enrolment into the sperm cryopreservation program; those in the latter category collected only one or two samples. A brief medical history including their diagnosed cancer type was obtained from all patients and blood samples were screened for infectious diseases.

The initially collected semen samples were analyzed according to World Health Organization guidelines for concentration and motility (19) and strictly according to Kruger et al. criteria for morphology (20).

The semen sample was cryopreserved only if motile spermatozoa were found regardless of its concentration. Upon assessment, the semen sample was diluted 1:1 with cryoprotectant (test-yolk buffer with glycerol). Aliquots of 1 mL were transferred to screw-top plastic vials and subjected to a slow cooling rate process. Then, the mixture was frozen at -20ºC for 10 minutes and suspended in vapor phase nitrogen for 2 hours before being stored in liquid nitrogen until required.

A 200 µL aliquot was separately cryopreserved in the same way for post-thaw analysis 24 hours after. To conduct the post-thaw analysis, samples were thawed at room temperature for 5 minutes, followed by 37ºC incubation for 5 to 10 minutes. The samples were washed with culture medium, and the concentration and motility were evaluated according to WHO guidelines for concentration and motility (19).

Data collected from 98 male cancer patients whose sperm samples were banked at our center consisted of the following: (i) Recorded parameters routinely inserted into our center's data bank (male age, marriage and parental status, type of cancer and treatment, period from cancer diagnosis to sample cryopreservation), (ii) The semen characteristics, (iii) The destinations of sperm banked samples (disposed of, thawed for our own use, or continuous cryopreservation), and (iv) Questionnaire responses provided by the volunteers themselves regarding their worries of fertility preservation and concerns about sperm banking.

Statistical analysis of the data was performed using the statistical package SPSS v14. The continuous data were expressed by mean ± standard error of the mean (SE) and compared between two groups using the Mann-Whitney test, or for multiple groups, analysis of variance (ANOVA). Categorical data were analyzed using frequencies and the chi-square estimation. P values < 0.05 were considered statistically significant.

RESULTS

Ninety-eight patients were referred for sperm banking before gonadotoxic therapy. The mean age was 33 years (range: 16-69 years) at the time of cryopreservation. The higher percentage of patients forming this cohort were diagnosed with testicular cancer (56.1%, n = 55), followed by prostate cancer (15.3%, n = 15), Hodgkin's lymphomas (9.2%, n = 9), non-Hodgkin's lymphomas (7.1%, n = 7), leukemia (3.1%, n = 3) and other malignancies (9.2%, n = 9), which included bladder, stomach, rectum, bone and lung cancers. All semen samples provided motile spermatozoa and therefore were suitable for cryopreservation.

Semen characteristics at the time of cryopreservation for the complete group were as follows: mean sperm concentration (45.4 million/mL, range 0.1-368 million/mL), mean of sperm with progressive motility (43.8%, range 6-84%), and mean of sperm with normal Kruger's morphology (3.5%, range 0-11%). The post-thaw test showed mean of motile sperm recuperation at 28.5%.

Patient ages and semen features along with cancer type are shown in Table-1. The patients with prostate cancer were older than patients of other groups. The semen analysis of patients in the testicular cancer group presented lower sperm concentration than patients in other groups, except those with non-Hodgkin's lymphoma.

The overall mean time between cancer diagnosis and sperm cryopreservation was 4.5 months. Although we had not observed a statistical significance, a shorter time between diagnosis and semen cryopreservation was observed for patients with testicular and prostate cancers (Table-1).

Also, the patients were classified according to sperm concentration as normozoospermia (defined

Table 1 *– Semen characteristics among male cancer patients prior to therapeutic treatments.*

Semen Characteristics	Testicular Cancer	Prostate Cancer	Hodgkin's Lymphoma	Non-Hodgkin's Lymphoma	Leukemia	Other Malignancies
N	55	15	9	7	3	9
Age (years)	28.9 ± 0.9 [a]	54.5 ± 2.9 [a,b,c,d,e]	27.3 ± 3.7 [b]	28.4 ± 1.3 [c]	28.3 ± 2.9 [d]	32.2 ± 3.7 [e]
Time between cancer diagnosis and sperm cryopreservation (months)	1.6 ± 0.3	1.8 ± 0.5	4.5 ± 4.4	5.1 ± 4.3	2.6 ± 1.7	2.6 ± 1.0
Sperm concentration (million/mL)	26.1 ± 3.2 [f, g, h]	71.7 ± 18.5 [f]	101.8 ± 43.3 [g]	48.3 ± 8.3	59.3 ± 11.8 [h]	57.6 ± 32.0
Total motility (%)	58.02 ± 2.0	50.9 ± 4.2	62.8 ± 3.8	66.4 ± 4.7	50.0 ± 21.5	48.8 ± 5.9
Progressive motility (%)	44.9 ± 2.3	35.9 ± 4.6	51.5 ± 5.1	54.7 ± 6.5	43.0 ± 18.3	34.8 ± 6.4
Kruger morphology (%)	3.3 ± 0.3	3.2 ± 0.6	3.6 ± 1.4	4.8 ± 0.8	4.7 ± 2.0	3.4 ± 1.4
Motile sperm recuperation post-thaw (%)	29.8 ± 3.6	19.6 ± 3.5	38.9 ± 11.4	36.8 ± 11.3	31.3 ± 20.4	16.1 ± 8.4

Values are mean ± standard error of the mean (SE). Mann-Whitney test = a, b, c, e: $p < 0.001$, d: $p = 0.011$, f: $p = 0.042$, g: $p = 0.016$, h: $p = 0.041$.

as sperm count ≥ 20 million/mL; 59.2%), oligozoospermia (defined as sperm count > 5 million/mL and < 20 million/mL, 20.4%), or severe oligozoospermia (defined as sperm count ≤ 5 million/mL, 20.4%). However, there was no difference as regards distribution of study patients grouped by cancer types ($p = 0.185$).

The social characteristics of patients showed that only 20.0% of them were married and had children, 28.0% were married and did not have children, and 52.0% were single and did not have children at the time of sperm cryopreservation. The prostate cancer group had a higher percentage of patients who were married (73.3%) and had children (50%).

After sperm cryopreservation, 39.0% of the patients received chemotherapy and/or radiotherapy treatment, 35.4% underwent surgery, and 25.6% had surgery followed by chemotherapy or radiotherapy.

The analysis of responses to the questionnaire item on cryopreservation time revealed that 78.8% of patients were aware of their fertility status. The group who expressed being the least concerned with fertility was the prostate cancer group (46.2%), while 84.7% of the patients in the other categories expressed aware-

ness of their fertility status (p = 0.002). This observed difference may be attributed to prostate cancer patients being older (80% were 55 and older) and who already had children (50% of prostate cancer group).

Overall, 86.9% of the study patients ranked fertility as an important issue following cancer treatment. While many of them already had children, 86.6% of all the study patients still reported infertility a post-treatment concern. Furthermore, 89.5% of them mentioned that they felt comfortable with semen cryopreservation regardless of the type of cancer with which they were diagnosed (p = 0.205).

The sperm samples were cryopreserved for a mean time of 52.7 months. At the time this report was drafted, 80 samples (81.6%) remain cryopreserved in our sperm bank. Sperm storage was discontinued for 18 patients (18.4%) upon the request of either the patient or his wife. At any time, study patients were able to request their own semen samples from our center for use in assisted fertilization techniques.

Between 1996 and 1999, 14 cancer patients agreed to sperm cryopreservation at our center. Since then, an average of 10.1 cancer patients cryopreserved sperm in our centre per year.

COMMENTS

In the present study, we retrospectively evaluated the semen characteristics and attitudes of male cancer patients who had sperm banked before cancer treatment.

Evidence suggested that cancer patients have an intrinsic suppression of spermatogenesis due to disease as oligozoospermia was more frequently observed. The exact mechanism for this suppression is not well established (21). On the other hand, the patients who suffer from testicular cancer showed higher semen abnormalities, probably related to the neoplasm itself (4,11).

Although many studies have reported azoospermia in cancer patients (11,22), all the patients in the present study provided motile spermatozoa and therefore were suitable for cryopreservation. Our findings also demonstrated that the percentage of oligozoospermia in male cancer patients was high (40.8%) independently of cancer type. However, an examination of the sperm concentration revealed that it is significantly lower among testicular cancer patients; thus, this finding supports our hypothesis that the cancer itself influences spermatogenesis generally and is amplified in testicular cancer patients.

The decline in semen quality following thawing is dependent on its initial quality before freezing, but some studies have demonstrated that the cryopreservation process itself does not affect spermatozoa of cancer patients any more than that of healthy donors (23). In this study, we observed a mean post-thaw recuperation rate of 28.5%.

In 2008, it was estimated that there will be 238,860 new cases of male cancer in Brazil, and 120,330 in the State of Sao Paulo state (24). Our center serves the State of Sao Paulo. Over a period of 12 years, only 98 cancer patients cryopreserved semen samples before cancer treatment. This is, in fact, representative of sperm banking in Brazil where the number of centers offering sperm banking is small, and only a limited minority of patients ask for sperm banking.

In our study, testicular cancer patients more frequently requested sperm cryopreservation, followed by prostate cancer patients. Also, we found that the mean time from diagnosis of cancer to the semen collection to cryopreservation was 4.5 months, but this period for testicular and prostate cancer patients was shorter. Reasons for this observed difference may be a higher level of awareness of the need for sperm banking by the medical team treating patients with cancer of the reproductive organs, or by the patient himself, who then influences the awareness level of the cancer site regarding fertility issues.

Some authors have raised doubts about the justification and necessity of providing the facilities for banking spermatozoa before chemotherapy (25), specially for the reason that the relatively small number of men making use of it following completion of treatment is less than 10% (26). The lack of sperm banking that was offered may be explained by several reasons: recovery or waiting for possible recovery of gonadal function, short period from original illness, anxiety regarding potential risks for the children and uncertainty about their long-term health and therefore their suitability to be parents (18).

In addition, a lack of discussion time, presumed high cost, unavailability of adequate facilities and overestimation of the limitations of sperm quality were the most reported reasons why sperm banking was not suggested (27).

At our center, the cost of sperm banking, including three samples of semen, is approximately U$ 500.00, with additional U$ 140.00 per semester for maintaining the cryopreserved sample; and for Brazilian patients, these costs are high.

Cancer patients can lose interest in preserving fertility when they are faced with an unpredictable and unfavorable prognosis. The collection of ejaculate is often difficult due to poor general health condition. The oncologist may also take a pessimistic view of survival rate for patients with aggressive cancer, thus diminishing the likelihood of sperm banking (28).

The most common reason for failing to bank sperm is a lack of awareness that such an option exists. Instead, many patients are left with significant anxieties over reproductive health concerns (28). On the other hand, assuring a patient that his fertility potential is secured by sperm banking could help in the emotional battle against cancer (29).

In this study, we found that most of the study patients were aware of fertility issues, that they expressed post-treatment infertility as an important concern, and that they were comforted by sperm banking as a means of fertility preservation.

Increasing awareness and the use of assisted reproductive technologies need to be promoted by an interdisciplinary team of experts caring for adolescents and young adults, as sperm cryopreservation is an efficacious method for preserving future fertility (30). All male cancer patients of reproductive age who will have treatment that may affect testicular function should have their sperm cryopreserved before the initiation of therapy.

Among the study cohort, less than 20% of banked sperm samples were disposed of upon the request of either the patients or their spouses. Reasons for disposal of sperm sample were patient death, no plans for more children, and recovery of fertility. However, at our center, we do not actively follow-up patients after completion of their cancer treatment; therefore, we do not have data on their survival or whether they have been able to conceive spontaneously.

While fertility preservation for post-pubertal male cancer patients has been well established (with sperm banking and techniques of assisted reproduction), there is little agreement regarding appropriate indications for and methods of gamete preservation in pre-pubertal boys (31). For pre-pubertal boys, the prevention of sterility in childhood cancer survivors given the existing practices is a clinical challenge since no active spermatogenesis is yet present. A promising advancement that has been proposed in the scientific community is cryobanking of testicular tissue as an acceptable strategy (32). However, this proposal faces a wall of ethical research debates regarding the conduct of experimentation on pre-pubertal individuals.

Comprehensive cancer treatment planning is needed to help oncologists offer sperm banking as an option to all men at risk of infertility, due to cancer itself or its treatment. The improvement in cancer treatment and life expectancy, combined with greater awareness for fertility options, careful reassurance of the survivors regarding the safety of their children, the possibility of infertility treatment by assisted reproductive technology, and the beneficial contribution in the emotional battle against cancer all lend support to routinely offering sperm banking to all cancer patients, especially those who are interested in having children with their partners.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

The article by Bonetti and colleagues highlights the importance of understanding and awareness of the benefits of sperm cryopreservation in a multi-disciplinary team of health care professionals. Our experience in Canada from a retrospective chart review (1) illuminated the fact that we needed to address the multi-disciplinary team to negate the gap in complimentary service between health care professionals in both cancer and fertility specialties.

Our research partnership aimed at increasing the use of fertility preservation strategies. Following an extensive literature review we formed our framework. The need for heightened awareness of the opportunities for patients to preserve their fertility then became our focus. It was quickly determined that we needed to have a two-pronged approach to solving this dearth of information. One would focus on the allied health care professionals while the other would focus on the patient.

The first step in this process focused on empowering staff to ensure referrals were made to the Fertility Clinic. An algorithm for identifying patients was developed to aid in the identification of candidates for fertility preservation sooner rather than later in treatment. This afforded the patient the appropriate time to consider his fertility preservation option(s) and still have the time to bank samples prior to treatment. In addition, creating a standard referral approach facilitated staffs' discussions and eased their discomfort about discussing sperm banking, especially among younger patients. Increased awareness and more rigorous clinical approach including the use of the Referral Form resulted in a 71% increase in sperm cryopreservation referrals compared to the previous year.

A further project investigated Nurses' perception(s) of discussions with patients regarding the patients' future fertility (2). An underlying purpose of this study was to determine any communication barriers and to ascertain what type of educational materials would be beneficial.

Since the use of sperm banking, as part of the treatment protocol for adolescent and young adult (AYA) males with cancer, requires the expertise and cooperation of a multidisciplinary team of oncology and fertility experts nurses' have a primary contact with patients, their role in effective communication information to patients is crucial. Therefore, patients' awareness and understanding of sperm banking is a key element to success. Patients need to make in-

formed decisions at a time when they are inundated with treatment information.

A parallel consideration is the fact that the ability for a cancer survivor to one-day has their own family is of paramount importance to their quality of life during and after treatment. With this in mind, "plain language" education materials were developed to adequately inform male AYA oncology patients about sperm banking prior to cancer treatment (3). The project involved a collaborative partnership among health professionals from both the cancer and fertility clinics.

The educational brochures are beneficial for initiating discussion with the patient. Using the educational brochure as a teaching tool has led to the development of expertise and high comfort level among staff and expertise in facilitating these sensitive discussions. The key points in this process are listed below, and have become part of the routine standard of care: 1) Ensure that the health care provider gives all the appropriate information to the patient so that the patient can make an informed decision and be successful in providing an ejaculate for banking, 2) Ease the discomfort that is often felt by health care providers when discussing sperm banking, 3) Provide a timely referral to the fertility clinic.

Adolescents and young adults with cancer are a unique group. Due to many external factors and changes that take place during this time in their lives the diagnosis of cancer can be overwhelming. Providing AYAs with evidence-based information about fertility preservation by staff trained to impart this information allows them to make informed decisions about their fertility preservation options. Our framework for coordinating efforts in providing fertility preservation options to patients undergoing treatment for cancer encourages the use of effective multi-disciplinary teams that include: oncologists; nurses in both specialties of oncology and infertility, social work, reproductive endocrinology and infertility specialists, andrologists, and embryologists are required to work together in order to achieve success. The result of this unique team approach is not only a cancer survivor but one that is able to round out their quality of life by being able to have a family of their own.

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Robotic-Assisted Partial Nephrectomy: Surgical Technique Using a 3-Arm Approach and Sliding-clip Renorrhaphy

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ABSTRACT

Introduction: For the treatment of renal tumors, minimally invasive nephron-sparing surgery has become increasingly performed due to proven efficiency and excellent functional and oncological outcomes. The introduction of robotics into urologic laparoscopic surgery has allowed surgeons to perform challenging procedures in a reliable and reproducible manner. We present our surgical technique for robotic assisted partial nephrectomy (RPN) using a 3-arm approach, including a sliding-clip renorrhaphy.

Materials and Methods: Our RPN technique is presented which describes the trocar positioning, hilar dissection, tumor identification using intraoperative ultrasound for margin determination, selective vascular clamping, tumor resection, and reconstruction using a sliding-clip technique.

Conclusion: RPN using a sliding-clip renorrhaphy is a valid and reproducible surgical technique that reduces the challenge of the procedure by taking advantage of the enhanced visualization and control afforded by the robot. The renorrhaphy described is performed under complete control of the console surgeon, and has demonstrated a reduction in the warm ischemia times in our series.

Key words: *kidney; nephrectomy; surgical procedures, minimally invasive; robotics*
Int Braz J Urol. 2009; 35: 199-204

INTRODUCTION

The diagnosis and treatment of renal tumors has evolved over the last 15 years, spurred by the increased incidental detection of small, asymptomatic renal masses on abdominal imaging, as well as by the widespread adoption of nephron-sparing surgical techniques. Even for patients with normal renal function, nephron-sparing techniques have been advocated whenever feasible due to the low morbidity and excellent long-term functional and oncological outcomes (1).

The constant search for solutions that combine optimal outcomes with less inconvenience for the patients, better cosmetic results, and shorter hospitalization has lead to the validation of laparoscopic partial nephrectomy (LPN) as a viable and acceptable alternative to traditional open partial nephrectomy (OPN) (1). However, the major obstacle to the widespread use of LPN is its technical difficulty and steep learning curve, particularly with regards to renal reconstruction and intracorporeal knot tying, which are generally performed under the time constraints of warm ischemia.

The introduction of robotics into urologic laparoscopic surgery has provided remarkable enhancements to minimally-invasive procedures by adding three-dimensional visualization, wrist-emu-

lated mobility for the instruments, better ergonomics for the surgeon, and the reduction of tremor. Several reported series have described various techniques for robotic partial nephrectomy, but commonly lack an appropriate description of an efficient, effective, and reproducible technique for renorrhaphy (2-3).

Sliding-clip renorrhaphy, a technique for renal reconstruction, was recently refined at our institution, and described in a prior report (4). Since its introduction in 2007 and display at the 2008 Worldwide Robotic Renal Symposium, it has been gaining acceptance due to its ease of implementation and quality of repair.

The objective of this report is to describe our technique for robotic-assisted partial nephrectomy (RPN) using a 3-arm approach, including the sliding-clip renorrhaphy technique.

SURGICAL TECHNIQUE

Under general anesthesia, the patient is placed in a flexed, full flank position. A Veress needle is used to establish a pneumoperitoneum of 15 mm Hg. A 12 mm camera port is placed approximately 2 to 5 cm superior to the umbilicus. Under direct vision, the 8 mm robotic trocars are placed, one subcostal and one in the lower quadrant. This provides appropriate triangulation of the instruments. A 12 mm assistant port is placed in between the robotic trocar sites, cephalad or caudal depending on the tumor location, and at least 1 cm below the plane of the camera port. For right-sided masses, a 5 mm subxiphoid trocar can be placed for liver retraction if necessary (Figure-1). The robot is then docked at an angle, centered along the line defined by the camera port and the renal hilum.

For this approach, a 30-degree down lens is used. The robotic instruments used include monopolar scissors, Prograsp forceps, and robotic needle drivers. The assistant's responsibilities include retraction and clearing of the field with a laparoscopic suction device, as well as placing bulldog clamps for hilar control, and passing Weck (Teleflex, Research Triangle Park, NC) Hem-o-Lock clips and LapraTy (Ethicon, Cincinnati, OH) clips utilized during the renorrhaphy.

The kidney is exposed by incising the peritoneum sharply along the white line of Toldt and reflecting the colon medially to provide optimal exposure of the retroperitoneal space (Figure-2). Next, the ureter, gonadal vessels, and the lower pole of the kidney are identified and retracted laterally, placing the renal vessels on stretch, a maneuver that aids the hilar dissection. The identification of the hilar structures is performed using standard laparoscopic techniques. The isolation of renal artery and vein is necessary for selective vascular clamping, and is achieved by gently pushing the fat off both the front and the back of the vessels (Figure-3).

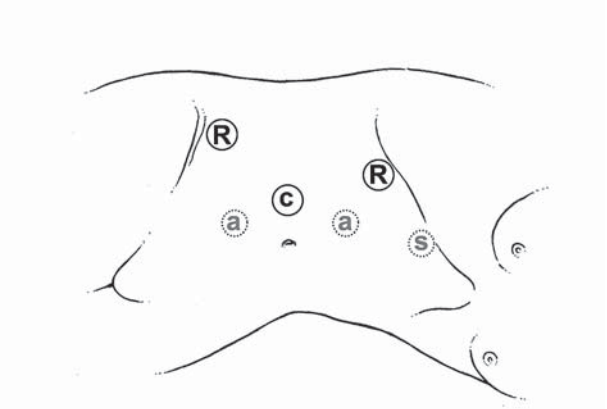

Figure 1 *– Trocar positioning for the 3-arm approach. C = Camera port (12 mm), R = robotic arms (8 mm), a = alternatives for assistant trocar (12 mm), s = additional port for liver retractor (5 mm).*

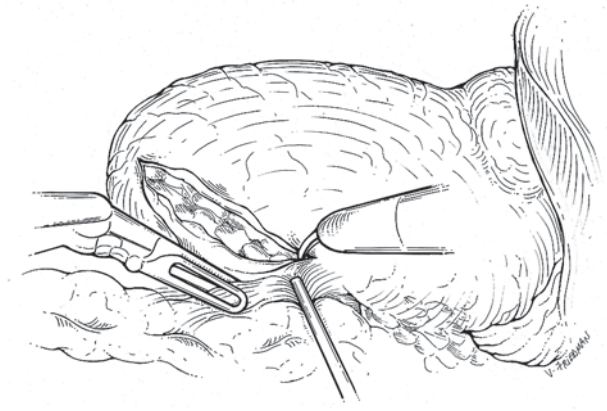

Figure 2 *– The kidney is exposed by reflecting the colon medially.*

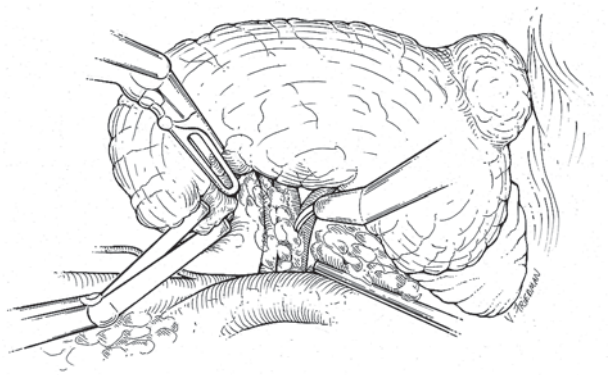

Figure 3 *– The kidney is retracted laterally to allow adequate exposure and aid hilar dissection.*

Next, attention is focused on tumor localization. If necessary, the kidney can be mobilized for upper pole or posterior tumors. For both endophytic and exophytic tumors, an ultrasound is performed to define the extent of the mass. The fat overlying the normal parenchyma is dissected free; however, the fat overlying the mass is left intact for pathologic analysis. The capsule of the kidney is scored with cautery (Figure-4).

Vascular clamping is performed with bulldog clamps placed by the assistant after mannitol (12.5 or 25 gm) infusion. In our technique we prefer arterial and venous clamping separately, ensuring a bloodless field during the resection (Figure-5). Renal ischemia is confirmed by evaluating the change in color, size, and consistency of the kidney.

Tumor excision is then performed following standard oncological principles, preferentially with monopolar scissors and the aid of the assistant's suction for providing countertraction and maintaining a dry field. Once complete, the specimen is placed beside the kidney or on the top of the liver for later retrieval. Biopsy samples are obtained by the assistant from the surgical bed and sent for frozen section analysis.

For the reconstruction phase, the scissor is exchanged for a needle driver, and the Prograsp is retained for use in tightening sutures. Adequate hemostasis is then achieved using cautery and, in some cases, placing figure-of-eight sutures to address larger veins or arteries. If the collecting system is entered during the excision, it is oversewn with 2-0 polyglactin on an SH needle, and a LapraTy clip may be used to secure the suture. In select cases, we use a bolster of thrombogenic material that is placed to fill the renal defect.

The renorrhaphy is performed using a sliding-clip technique, which is described in detail elsewhere (4). Zero or No. 1 polyglactin sutures on a CT needle are prepared on the back table by cutting to a length of 15 cm, and tying a knot at the end. A LapraTy clip

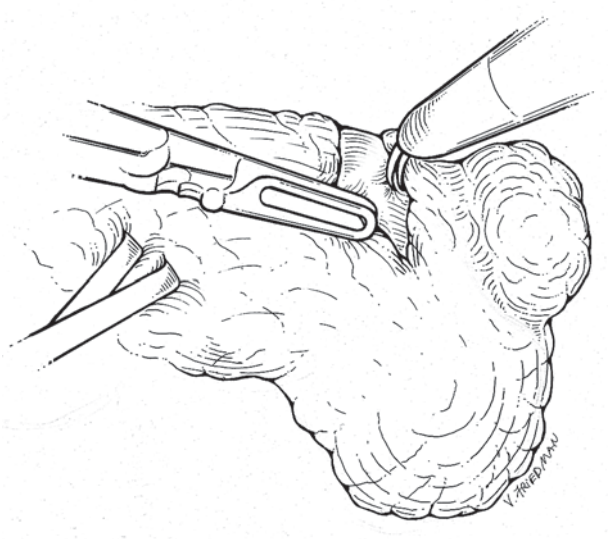

Figure 4 *– Renal mass identification and determination of margins of resection.*

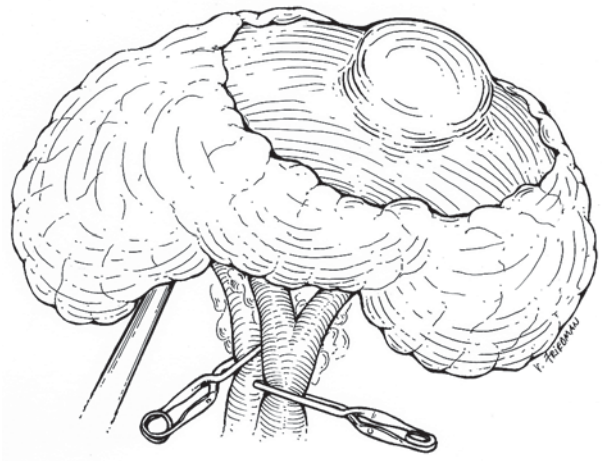

Figure 5 *– Selective vascular clamping with bulldogs prior to resection.*

is placed above the knot, followed by a Weck Hem-o-Lock clip. These sutures are then placed through the margins of the capsule at intervals of 1 cm. After the final throws have been completed, the assistant places a Hem-o-Lock clip on the loose end of the suture. The surgeon seated at the console is then able to slide the clip towards the repair zone to tighten the renorrhaphy under precise control, allowing for a secure, hemostatic closure. In addition, the tension of the repair can be re-adjusted as necessary. When the optimal closure has been achieved, a LapraTy clip is applied to lock the sliding clip in position (Figure-6).

The hilum is then unclamped, starting with the vein, and then the artery. If bleeding occurs after unclamping, it is initially observed as a re-expansion of the perfused kidney which may lead to further tension on the repair, resulting in tamponade. If bleeding persists, the clips may be re-tightened or additional sutures may be added. The use of hemostatic sealant agents is optional, and depends upon the surgeon's preference and size of the defect.

The specimen is then placed in a retrieval bag for extraction using one of the trocar sites. The perirenal fat is repositioned over the kidney and usually secured by placing a Hem-o-Lock clip. If there are concerns over collecting system injury, a closed suction drain may be placed, but is not necessary in all circumstances. Finally, wounds are closed with subcuticular sutures.

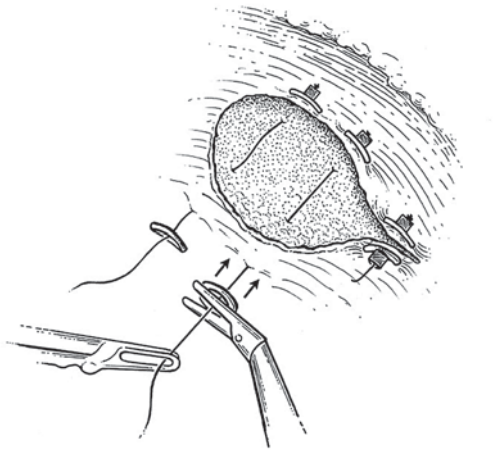

***Figure 6** – Sliding-clip renorrhaphy.*

COMMENTS

Minimally invasive nephron-sparing techniques, which have been developed for the treatment of renal tumors, are based on the gold standard of open partial nephrectomy. The surgical principles for identification, dissection, vascular clamping, and resection are essentially the same in all approaches. However, renal reconstruction is more difficult for pure laparoscopic techniques, owing to the confined space, restrictive working angles, limitations of the instruments, two-dimensional view, and reduced tactile awareness, all of which are further exacerbated by the need to limit warm ischemia times.

The use of robotics in laparoscopic surgery aims to solve many of these problems. As previously described, the enhanced stereoscopic visualization and instrument mobility can reduce many of the challenges common to the laparoscopic approach to a considerable degree. Nevertheless, the majority of the techniques for renorrhaphy described in the literature for LPN and RPN are similar, and mimic those used in OPN.

The renorrhaphy technique employed at our institution is a simple, reliable, and reproducible way to achieve an optimal surgeon-controlled reconstruction, which takes advantage of the precision offered by the robotic instruments. The sliding-clip technique provides an efficient and effective closure, which obviates the need for intracorporeal knot tying, and offers the ability to re-tighten the sutures if necessary to ensure proper tension. This technique has been used in the majority of our RPN and has been adopted as the standard renal reconstruction by all surgeons involved in our institutional robotic renal surgery program. Further implementation and its routine use has demonstrated a decrease in the warm ischemia time in comparison with our series of LPN (25 min for LPN v/s 19 min for RPN) (5); and also a similar trend of decrease can be observed when we compare the now standardized procedure with our initial experience of 13 RPN, when the traditional knot-tying and clip closure was used for reconstruction (24 min. for traditional v/s 16 min. for sliding-clip renorrhaphy). However, a focused prospective analysis will be necessary to confirm if this trend is significant. A more detailed description

of our series and outcomes can be found in prior publications of our group (5,6).

RPN is a procedure that continues to evolve. Future improvements to the technique and technology are likely to address issues of exposure, vascular control and reconstruction. Many of these innovations are likely to arrive with the introduction of new instruments and combination with ablation techniques in development, which will further reduce the challenge of the procedure, allow for less reliance upon the assistant, and minimize warm ischemic times.

CONFLICT OF INTEREST

Dr. Sam B. Bhayani is a paid consultant of Intuitive Surgical, Sunnyvale, CA, USA.

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EDITORIAL COMMENT

Partial nephrectomy for renal tumors smaller than 4 cm of diameter is currently recommended with similar oncological long term outcomes of radical nephrectomy. However, it remains to be a challenging surgery for both conventional and laparoscopic methods, considering the preservation of the remaining parenchyma, intra and post-operative bleeding and post-operative urinary leakage.

This technical proposal for partial nephrectomy seems very promising and I had the opportunity to testify how elegant one sliding-clip renorrhaphy surgery was in a Robotic Brazilian Symposium in Sao Paulo a few months ago. The bleeding was minimal and the warm ischemia lasted for 20 minutes. However, some remarks should be made. The stitches were used in the same fashion as in pure laparoscopic procedure.

The only difference is the absence of tying knots. Intra-corporeal knot tying has become easier and faster with DaVinci robot. Therefore, why spend more money using Hem-o-Lok as well as LapraTy clip in sliding-clip technique for renorrhaphy? Using robot the time for knotting should not be so different from the time elapsed for applying these clips. I believe that maybe it is an alternative for cases when the estimated warm ischemia time might be higher than 30 minutes and perhaps more useful for pure laparoscopic partial nephrectomy especially for those surgeons with low familiarity in reconstructive laparoscopic surgery. Prior to be considered superior than intra-corporeal knot tying reconstruction, the results of both methods must be compared in a prospective analysis.

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REPLY BY THE AUTHORS

We sincerely appreciate Dr. Mitre's thoughtful comments, as he raises some very valid questions regarding our preference for sliding-clip renorrhaphy over a more traditional tied-suture reconstruction. We certainly agree that robot assistance significantly reduces the challenge of intracorporeal knot tying; however, due to the need for delicate handling of the renal tissue, coupled with the need to limit warm ischemic times, tied-suture renorrhaphy remains a relatively challenging technique in this setting.

During a tied-suture closure, the sutures are necessarily pulled at angles off the perpendicular, placing shearing forces upon the capsule, which may lead to inadvertent tearing, even with the use of pledgets. With sliding-clip renorrhaphy, all closing tension is applied perpendicular to the capsule, which we feel reduces the risk of capsular disruption. Moreover, the large footprint of the Hem-O-Lock clip distributes the tension evenly across a comparatively wider surface area, further minimizing the risk of capsular tear.

Furthermore, should the tension on the repair be found to be suboptimal, or if bleeding is encountered after the clamp is removed, sliding-clip renorrhaphy allows the surgeon to adjust the tension of the repair without the need for the placement of additional sutures, something which is not possible using a traditional tied-suture repair.

With regards to the expediency of sliding-clip renorrhaphy, we have recently reported our data demonstrating that the implementation of the sliding-clip technique for renorrhaphy is associated with significant reductions of both overall operative times, as well as warm ischemic times, with the latter being reduced by nearly 8 minutes (1).

Although a warm ischemic time of less than 30 minutes is generally considered safe in patients with normal preoperative renal function, the role of robot-assisted partial nephrectomy is ever expanding to include patients with increasing degrees of renal impairment and larger tumors. As such, any technique which may result in a reduction of warm ischemic times may prove critical to the continued success of the robotic approach.

Therefore, we believe that the disadvantages of a slightly higher cost are more than offset by the potential benefits to the patient in terms of maximal preservation of renal reserve. We however, agree that prospective analysis will be needed to further evaluate the utility of sliding-clip renorrhaphy.

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The Authors

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A New Extra-Abdominal Channel Alternative to the Mitrofanoff Principle: Experimental and Preliminary Clinical Experience

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ABSTRACT

Introduction: The appendix is the gold-standard channel for the Mitrofanoff principle in pediatric urology, but the search for alternatives is justified considering it may not be available or preferably used for colonic stomas (Malone antegrade continence enema). The aim of this study is to report on technical feasibility of a new approach for creating catheterizable channels in a rabbit model and to present our preliminary clinical experience.

Material and Methods: We configured a tube from two rectangular skin flaps 1x4 cm opposite each other in the middle line of the lower inferior abdomen. The channel was anastomosed to the bladder dome with embedding sutures to create a valvular mechanism. The experimental study consisted of 12 rabbits, divided in 4 groups according to the sacrifice schedule at 2, 4, 8 and 12 weeks. At 30th postoperative day, an urodynamic evaluation was performed to record continence of the stoma. A histological analysis of the specimens stained with hematoxylin-eosin, Masson trichrome and Picrosirius red was also done in group 2 (sacrifice at 4 weeks postoperatively). We used this method in 3 patients with congenital non-neurogenic bladder disease presenting with massive residual volumes without compliance deficits.

Result: The technique proved feasible in all animals, 9 of 12 could be easily catheterized and underwent urodynamic study. No stoma leakage was observed in 7 animals at high bladder pressures (> 50 cm H_20) and only 2 animals had some leakage at 40 cm H_20. Urodynamics performed through the stoma showed urethral leakage at 20 cm H_20, therefore demonstrating the efficacy of the valvular mechanism. Histological analysis confirmed good integration between the tube and the bladder. Mean follow-up of the clinical series (3 patients) was 7.2 months. Two patients remained continent up to 4 hours, whereas 1 patient had some leakage after 2 hours.

Conclusion: We were able to confirm feasibility of a new extra-abdominal channel based on the Mitrofanoff principle and successfully reproduced the method in a clinical setting. Follow-up was short and long term results are required before any conclusive judgment can be made.

Key words: *bladder; children; urinary diversion; Mitrofanoff principle; surgery*
Int Braz J Urol. 2009; 35: 205-16

INTRODUCTION

The introduction of clean intermittent catheterization (CIC) at the 70s improved considerably the quality of life in patients with neurogenic bladder and other end-stage bladder disease (1). The appendicovesicostomy gave patients more comfort and autonomy, especially for those confined to a wheel-chair or boys with urethral sensitivity (2). The appendix is the gold-standard channel for urinary reservoirs but simultaneous need for a MACE (Malone antegrade continence enema) procedure and urinary reconstruction forced urologists to find alternatives to the appendix as the outlet tube. The Yang-Monti, double Monti and Casale tubes are good options but they still have complications and are constructed from

intestinal segments, which could be avoided when there is no need for bladder augmentation but only a Mitrofanoff channel in the native bladder (3).

A second point of concern in urinary and colonic continent stomas is the high incidence of stoma stricture, which might be related to variables like the technique itself, frequency of catheterization and presence of feces, although this latter condition has not yet been proved (4,5). To date, a revision rate of 10-50% due to stoma stricture has been reported in the literature.

The aim of this study was to report on technical feasibility of a new approach for creating catheterizable channels in a rabbit model and to present preliminary clinical results. The technique was named RPM because they are the initials of three authors who developed the concept (Rosito, Pires and Macedo). One possible advantage of this method is in cases where it is necessary to create an abdominal channel for catheterizing the native bladder without need of opening the peritoneum to obtain the appendix or make a Yang-Monti tube thus reducing considerably the morbidity of the treatment.

MATERIALS AND METHODS

We selected the rabbit for this experimental model because of its practical features, including ease of manipulation and familiarity of our group with this model in previous experimental studies. The experimental protocol was reviewed and approved by the Local Animal Research Committee. A total of 12 New Zealand White Rabbits, approximately eight weeks old and a weight of 2.5-3.0 kg were acclimated at the Experimental Research Animal Surgery Department for one week before the procedures.

The rabbits were anesthetized intramuscularly with ketamine hydrochloride (30 mg/kg) and xylazine (5 mg/kg), and local anesthetic (xylocaine) was used to perform a penile block. All animals were operated on under sterile conditions and under optical magnification (2.5X). We made two rectangular flaps (1x4 cm) both opposite each other in the middle line of the lower inferior abdomen (Figure-1A). The vascular structure of both flaps was kept intact by inferior superficial epigastric vessels and superficial iliac circumflex.

The cranial and lateral surface of the flaps was sectioned, giving it enough mobility to allow a 90-degree rotation. The horizontal superior border was moved to the vertical position close to each other. A 5.0 polyglicolic acid running suture was performed configuring a skin plate (Figure-1B). The next step consisted of an anastomosis of the lateral margins of the flaps using a 10F plastic tube as a mold in order to create a tube (Figure-1C).

A small abdominal incision to reach the bladder was performed and a 0.5 cm section of the anterior wall at the dome level of the bladder was performed (Figure-1D). The proximal end of the tube was anastomosed to the bladder by means of 6-8 5.0 polyglicolic acid sutures (Figures 2A and B). The continence mechanism of the channel was done by embedding it over 3, 4.0 poliglycolic acid sutures at the seromuscular wall of the bladder. The abdominal wall was closed in layers and the stoma consisted of the distal end of the tube, which was adapted to the wound margins without circular anastomosis (Figure-2C). The animals were kept in a warm room with ventilatory support until they were well awake. The channel mold was left intact for 7 days. The experimental study consisted of 12 rabbits, divided in 4 groups according to the sacrifice schedule at 2, 4, 8 and 12 weeks (groups 1 to 4 respectively).

We evaluated patency of the stoma and performed urodynamic analysis at sacrifice (group 1) or 30th postoperative day when animals were sedated with midazolam 0.02 mg/kg IM and a 10F plastic tube insertion was attempted (Figure-2D). At this moment, an urodynamic evaluation was completed using a Dynamed set, (Sao Paulo, Brazil). We catheterized the bladder initially through the urethra using a 4F catheter for filling the bladder and a second one via the stoma for recording bladder pressure. A rectal catheter with a balloon was used to record abdominal pressure. We changed the filling/recording function of catheters for subsequently evaluating continence through the urethra and stoma. In order to better define detrusor leak-point pressure (DLPP) through the stoma we performed manual compression of the urethra to avoid overflow through the urethra and created a “stress” study for the channel continence mechanism. Detailed results are shown in Table-1 and were compared statistically using a Chi-square analysis. Animals of group

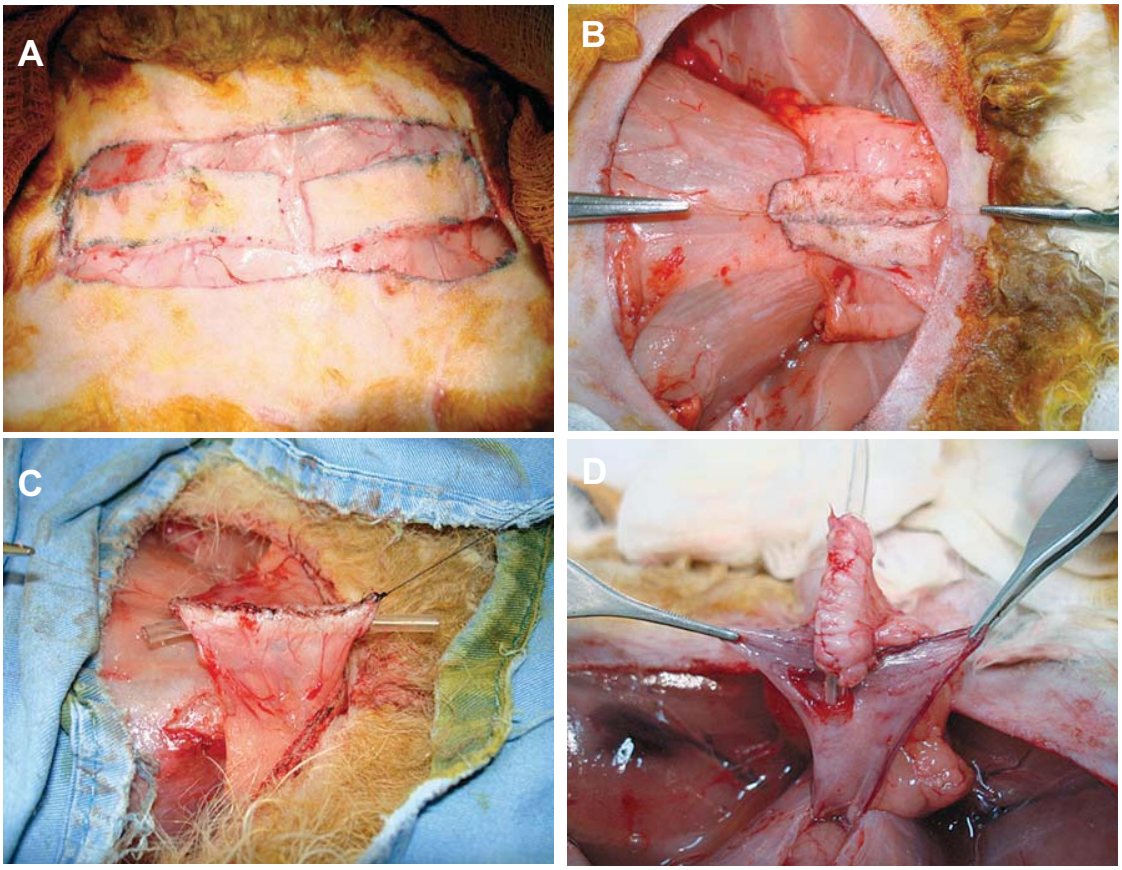

Figure 1 *– Two rectangular skin flaps 1x4 cm opposite each other in the middle line of the lower inferior abdomen are anastomosed as an "onlay" to create a tube to be connected to the bladder dome.*

2 were sacrificed and surgical specimens removed, fixed in formalin and sent for histological evaluation stained with hematoxylin-eosin, Masson trichrome and Picrosirius red.

After initial experience with the experimental model, we designed a clinical protocol and informed parents about potential advantages of the technique, mainly to avoid opening the peritoneal space and possible complications were also mentioned. The protocol was also approved by local Ethics Committee. We then introduced the method in clinical practice. We operated on three children presenting with non-neurogenic congenital bladder abnormalities presenting with massive residual volumes without storage deficiency. One patient had presumably primary bladder neck obstruction (Figures 3 and 4), one had posterior urethral valve and a third boy had prune-belly syndrome (Figure-5). Age at surgery and additional surgical procedures are described in Table-2. A stoma catheter (12F silicone Tube) was left indwelling for three weeks when a nurse-urotherapist trained patients how to perform CIC. Patients were followed as outpatients every month for at least 5 months for continence, urinary tract infection occurrence and stoma complications.

RESULTS

Experimental: There were minor complications related to the operative procedure in 2 cases: wound infection and partial wound dehiscence. At the sacrifice schedule for group 1 and 30th postoperative day for other groups, animals were examined as re-

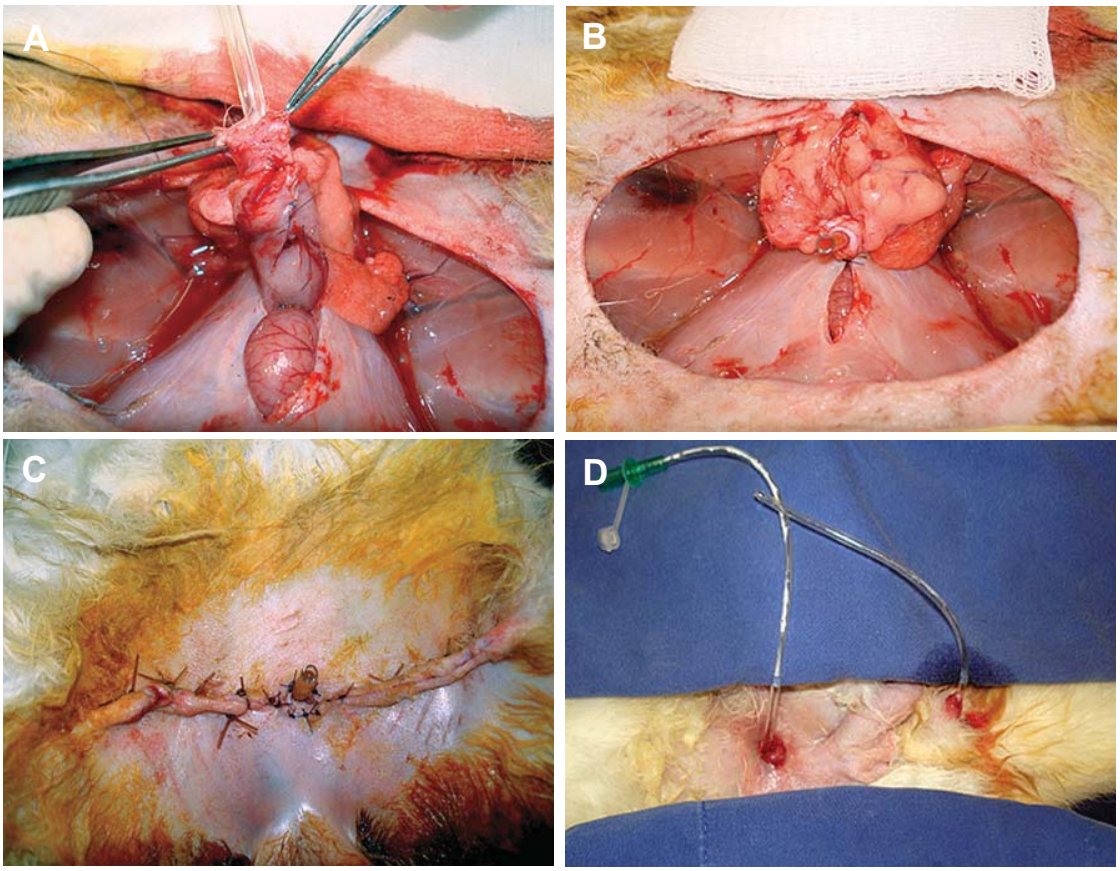

Figure 2 *– Anastomosis of the tube in the bladder and final aspect of the stoma. Notice that a catheter is inserted through the stoma and exits through the urethra proving patency of the channel.*

Table 1 *– Urodynamic records of postoperative evaluation at 30th postoperative day (except animals group 1).*

Animal	**UD per Urethra**			**UD per stoma**	
	DLPP ($cm\ H_20$)	**Maximal Pressure** ($cm\ H_20$)	**Cistometry** (mL)	**DLPP** ($cm\ H_20$)	**Cistometry** (mL)
1	40	50	80	20	30
2	40	60	70	20	20
3	No loss	110	100	20	30
4	No loss	100	70	20	30
5	No loss	65	100	20	30
6	No loss	100	80	15	25
7	No loss	60	80	15	20
8	No loss	60	100	20	30
9	No loss	60	80	20	25

DLPP = detrusor leak-point pressure.

gards the ease of catheterization, which was possible in 9 of 12 animals. The three failed cases included one animal with acute stricture of the stoma due to intense inflammatory response and the two others that developed wound dehiscence due to local infection.

Urodynamic evaluation was performed through both urethral and abdominal access at the same time. The detailed data are presented in Table-1. In summary, we found no leakage through the stoma in 7 of 9 animals reaching a detrusor pressure ranging from 60 to 110 cm H_20. The two other animals had leakage at 40 cm H_20. Maximal cystometric capacity ranged from 70 to 100 mL. In order to better evaluate the resistance pressure of the valve mechanism we had to perform manual compression of the urethra because urodynamics performed through a stoma catheter showed leakage at 15-20 cm H_20 through the urethra and no leakage at all through the stoma. These figures proved efficacy of the valvular mechanism of the tube when compared mean DLPP (or pressure at maximal capacity when no leakage occurred) in both situations ($p < 0.05$). An illustration of the urodynamic curve is shown in Figure-6.

The histological analysis of the specimen showed good integration of the skin tube with the bladder, in some areas with loss of epithelium however without ulceration (Figure-7).

Clinical: To date, our clinical experience of 3 patients presents good results with a mean follow-up of 7.2 months. Two patients manage to catheterize their bladders through their stoma 4-5 times a day without urinary leakage at 4 hour intervals. One patient (case 1) complained of painful catheterization and urinary loss after 2 hours interval between CIC after 5 months of uneventful outcome. In two cases,

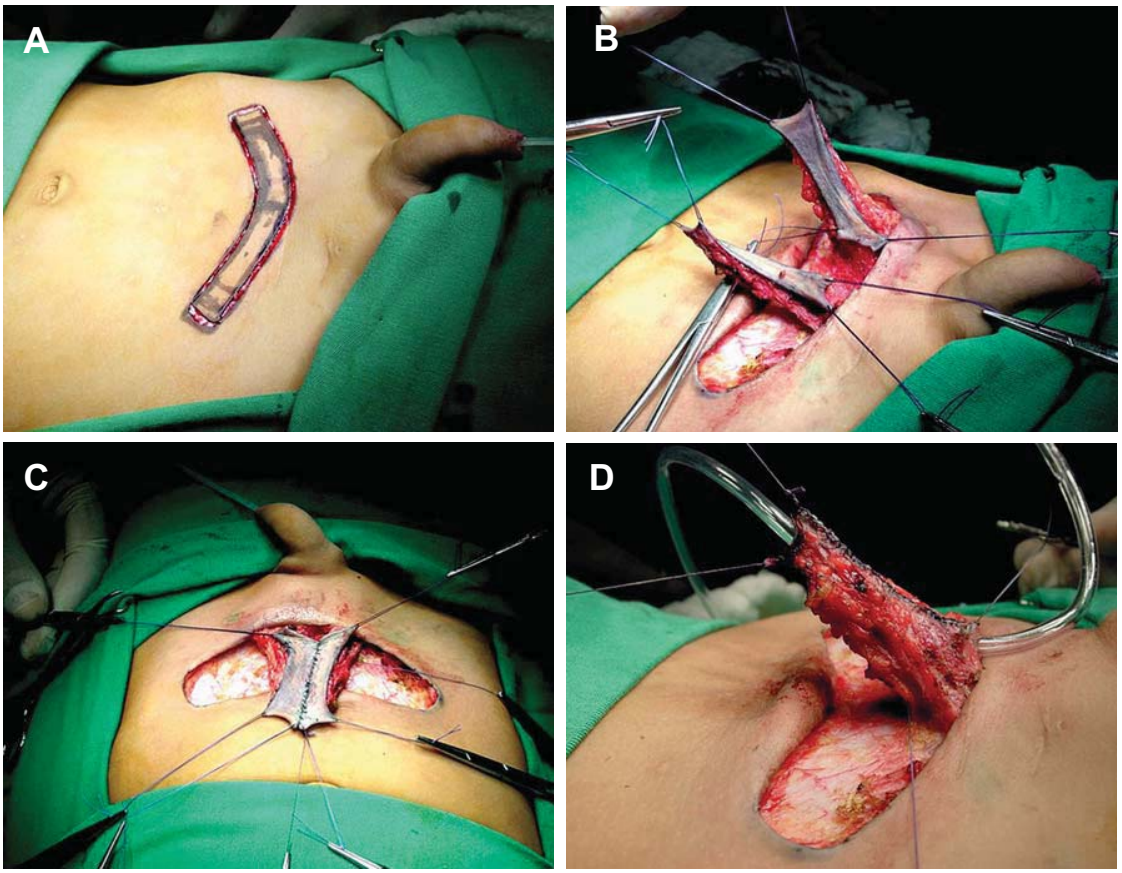

Figure 3 *– Construction of the tube with two skin flaps in the first patient operated with this technique.*

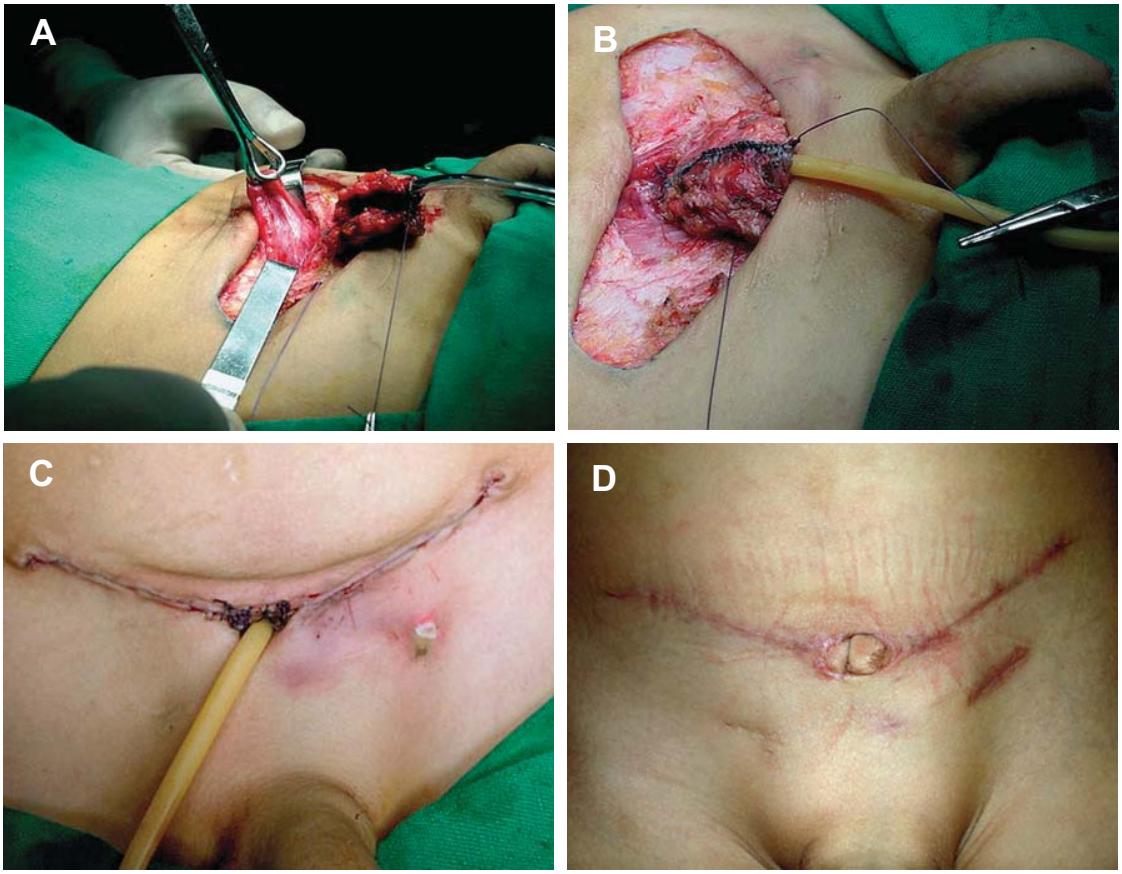

Figure 4 *– Anastomosis of the tube to the bladder dome and final aspect of the stoma at 60th postoperative day (Figure-4D).*

the RPM channel was performed with association of other procedures: a Cohen reflux repair and a Monfort abdominoplasty with orchiopexy.

COMMENTS

Continent urinary diversion requires an outlet that maintains continence but allows easy catheterization for voiding. Although none of the available options is ideal, the appendiceal flap-valve channel first described by Mitrofanoff appears the most reliable (1). Mitrofanoff principle is a well-established procedure in pediatric urology and main complications reported in the literature with this method are stoma stricture (8-39%), leakage (5-22%) and less frequently appendix necrosis and prolapse (3). In cases where the appendix is unavailable, ileum has been shown to be a suitable alternative. Although some studies have reported higher stoma complication rates with ileal catheterizable conduits, other studies have shown favorable results (2,3).

The Yang-Monti tubes, as well as their modifications, are the best alternative today specially for obese patients, however complications are even higher than the classical appendicovesicostomy and they require open access to the abdomen. This may not be a problem when bladder augmentation is also performed, but when the main problem is abdominal access for CIC the search for a better option is still justifiable.

The ureter has also been used to construct a Mitrofanoff channel. However, in the studies of Van Savage et al. (4) there was a higher risk of complica-

tions due to the need for associated ureteral reconstruction (reimplantation or transureteroureterostomy) as well as a greater risk of stoma stenosis.

The technique here presented based on two lower abdominal skin flaps (RPM) could also be regarded as a valuable alternative for continent urinary diversion, mainly because it is an extra peritoneal approach precluding intestinal opening and anastomosis, which theoretically could reduce clinical morbidity. A second potential advantage is the lower risk for stoma stricture, since the two flap anastomosis produce an "onlay" tube without circular anastomosis. If this hypothesis proves to be correct with long term follow-up this technique may gain acceptance especially because Thomas et al. (5) recently reported that up to 50% of stoma strictures are treated surgically.

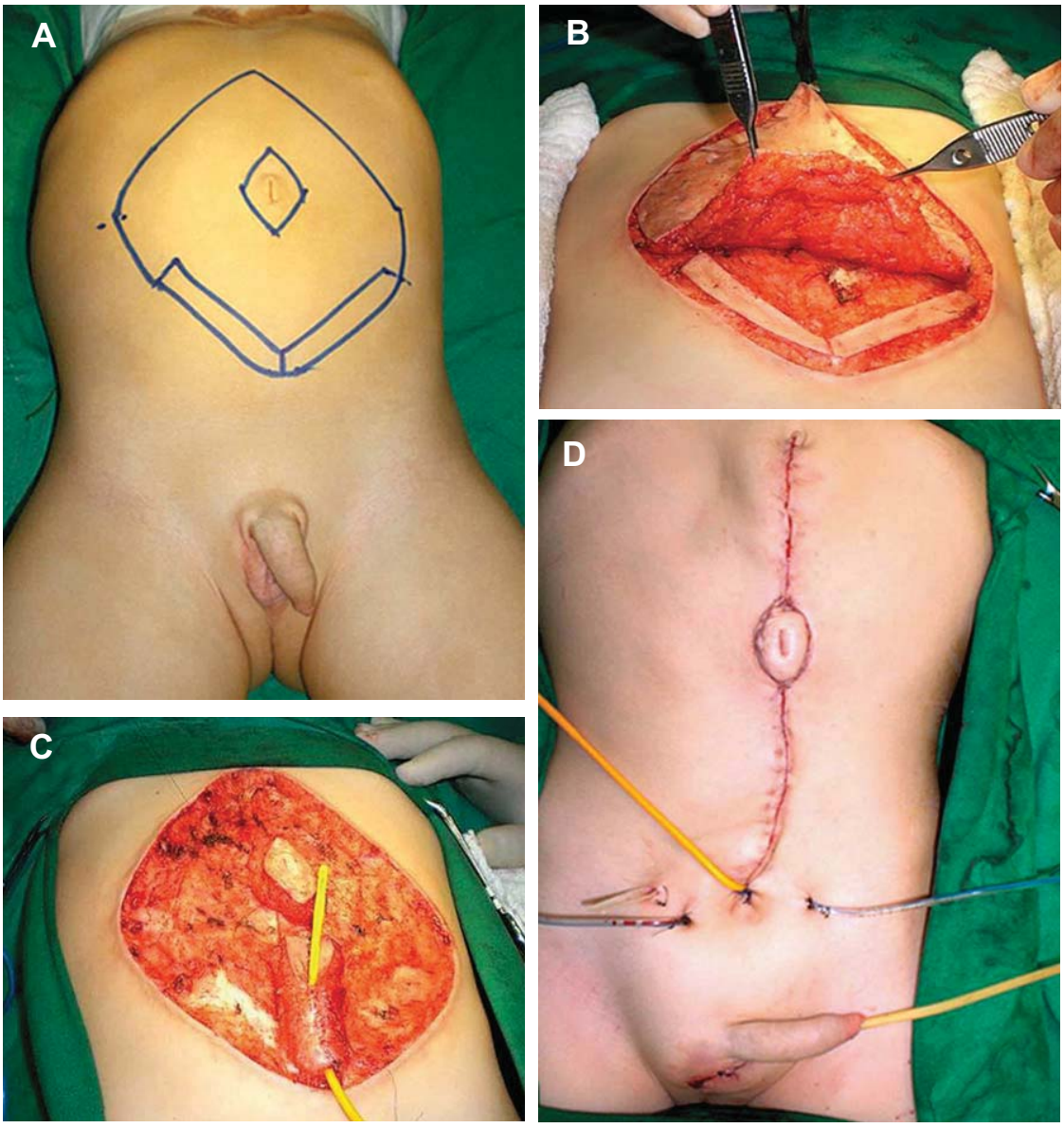

Figure 5 *– The technique associated to a Monfort abdominoplasty in one patient with prune-belly syndrome.*

Table 2 *– Clinical status of patients.*

Case	Age (years)	Diagnosis	Follow-up in Months	Additional Procedure	Present Status
1	4	Primary bladder neck obstruction	10	none	Painful catheterization, leakage after 2 hours
2	6	PUV	7	Cohen reflux repair	Continent > 4 hours
3	2	Prune-belly syndrome	5	Monfort abdominoplasty and bilateral orchiopexy	Continent > 4 hours

The inspiration for a two flap anastomosis to obtain a tube and not simply tubularizing one flap originated from the background of hypospadias repair that suggests that onlay repair is superior to one circular suture in terms of stricture rate. On the other hand, we also learned that these strictures may eventually occur with time and at the present moment we can not predict future of the tube described as a channel. During the peer-review process of this paper, one of the consultants mentioned a video available at the "you tube: http:// www.youtube.com/watch?v=56wNX4WKSro" with a similar but different concept of creating a neo-urachus by tubularizing a vertical flap of skin to communicate the bladder with the umbilicus. To our knowledge this procedure has not yet been reported in the literature and therefore we cannot comment on results or ethical aspects. It also differs from our technique as a circular anastomosis is used and theoretically more prone to stenosis or other complications.

We acknowledge that there other limitations of our study. The presence of hair in abdominal skin, mainly in males, could be a possible factor for producing stones. On the other hand, different from the urethra, urine will not be in permanent contact with the luminal surface of the tube, so we can not predict its evolution. We agree that the tube, if continent, might have a drop of urine deposited along the channel but mainly it is presumably only a conduit for CIC, and the role of skin inside the tube is not predictable. Some new methods of hair deepitelization with laser before surgery may also in the future prevent this complication, although there are not objective data currently available, to our knowledge, to support this procedure or its use only in selected cases after complications due to hair inside the channel.

We also acknowledge that vascular support of our channel, which is different from the appendix or Monti procedure originates from superficial vessels in the skin (epigastric and circumflex branches) so that caution should be observed in reoperations, although it would not limit any major abdominal operation when incision is performed above the stoma.

Our experimental data, in which an indwelling catheter in the channel could be left for only 7 days resulted in easy catheterization in 75% of cases (9 of 12). Histological evaluation confirmed good integration between the skin channel and bladder. Urodynamic evaluation confirmed efficacy of the valvular mechanism. The embedding sutures of the bladder over the channel created at least a 40 cm H_20 pressure resistance whereas urethral resistance recorded in the study was 20 cm H_20. Our group recently published an experimental ex-vivo model confirming efficacy of embedding sutures in creating resistance also in intestinal reservoirs and intestinal segments (6). We also applied this method for creating channel resistance in our concept of bladder augmentation or substitution over the past ten years (7). Our clinical series confirmed easy CIC in the three patients and continence with a mean follow-up of 7.2 months. Only one patient complained of pain during catheterization after 8 months with no abnormalities.

A third intuitive advantage of the method is the absence of wound skin anastomosis to the tube, since the tube is only adapted to the wound. We hy-

pothesized a possible impairment of stoma stenosis with our method. Overall, published stoma stenosis rates vary from 3% to 61% (8-10). Liard et al. (11) have the longest follow-up of 20 years and had stoma stenosis rates of up to 61%, compared with Horowitz et al. (12) who only had a 3% stoma stenosis rate, however, with only a short follow-up. Use of the cutaneous anastomosis technique with the incorporation of U-, V- or VZ-flap may also reduce stoma stenosis (13,14), however our method precludes any of these procedures and aesthetic aspect is also very favorable as seen in Figures 4D and 5D.

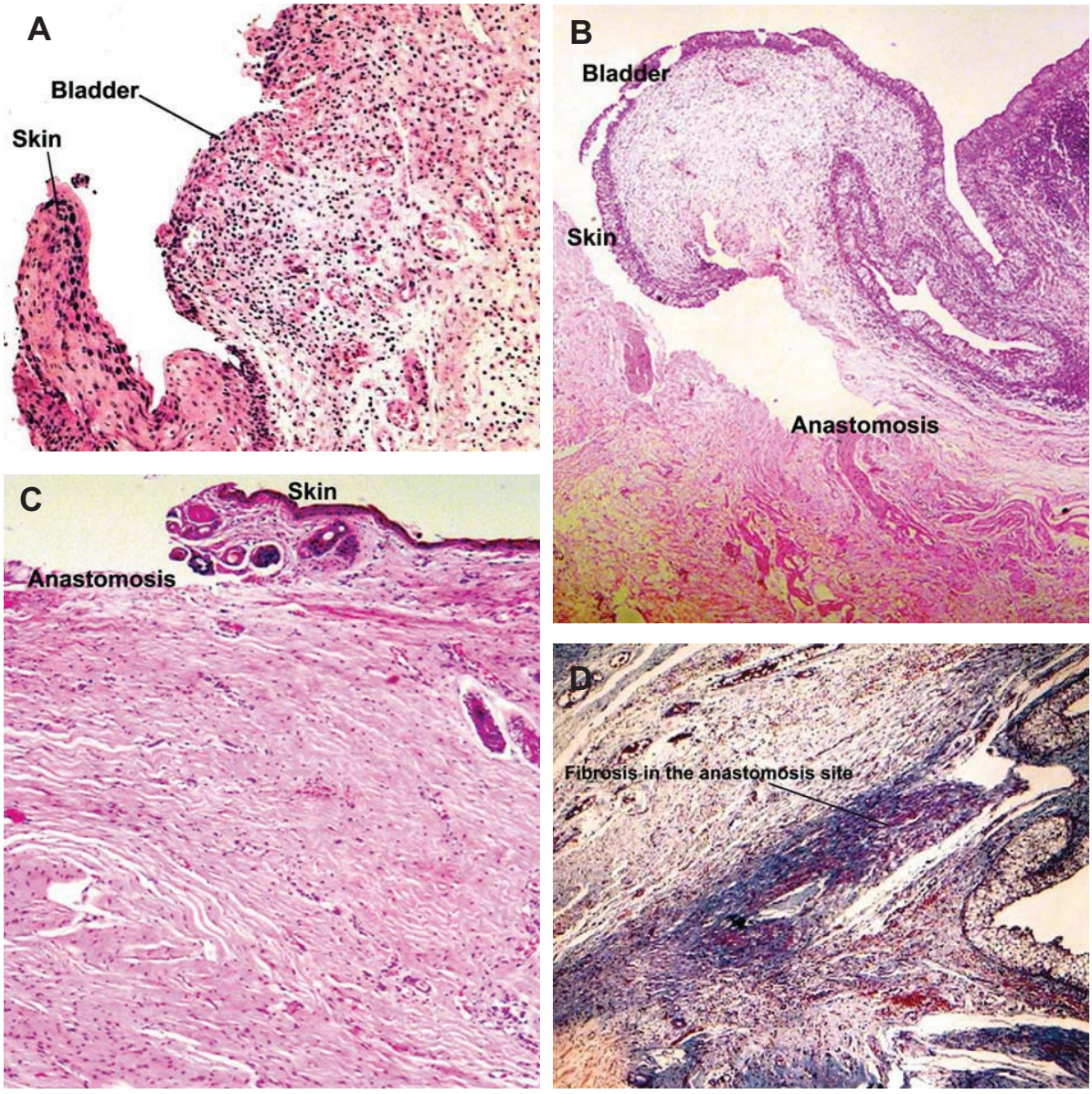

Figure 6 *– Histological analysis of the specimen showed good integration of the skin tube with the bladder, in some areas with loss of epithelium however without ulceration.*

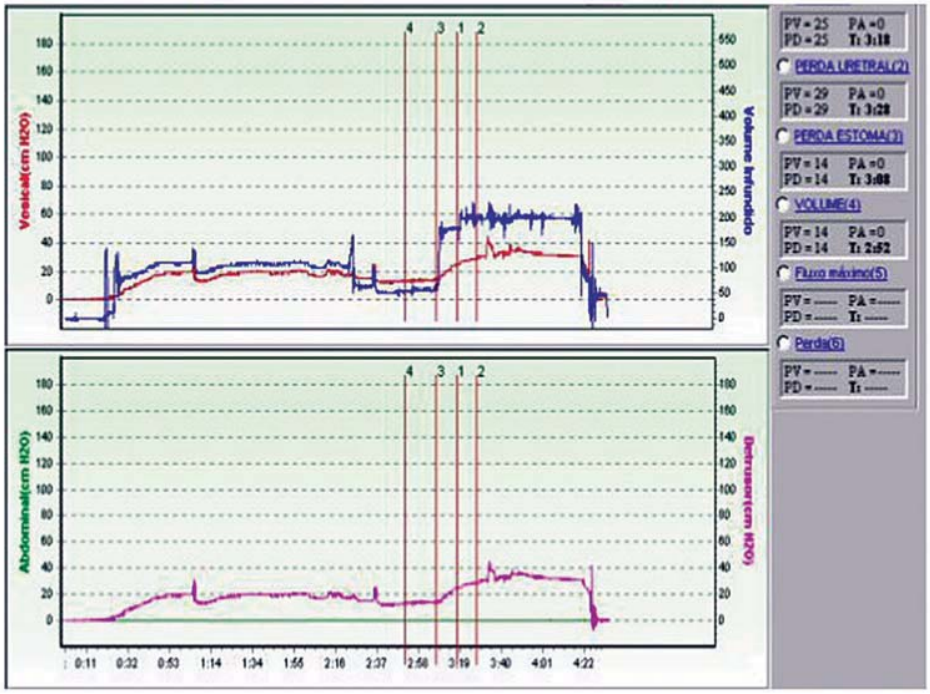

Figure 7 *– Urodynamic evaluation of detrusor leak-point pressure through the urethra (20 cm H_20: at first half of the examination) and subsequently through the stoma (40 cm H_20 with digital urethral compression: second half of the examination).*

In conclusion, we report our experimental and preliminary experience with a new approach for extra-abdominal channel construction based on the Mitrofanoff principle. The main advantages of our approach are the easy of the technique, applying well-known principles of onlay skin flap anastomosis like in hypospadia repair, minimal invasive access (extra-peritoneal) to the bladder and no need of skin flap anastomosis to the channel (possible impairment of stoma strictures). Long term results are definitely required before any conclusive judgment but preliminary results are very favorable and technical feasibility of the method could be proved in the experimental study.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

The article by Macedo et al. in this issue of the International Braz J Urol provides us with an interesting addition to the surgical armamentarium for fashioning continent catheterizable abdominal channels, further expanding the options that followed Mitrofanoff's groundbreaking contribution. This work provides exciting data on animal experiments that translated into therapeutic interventions in a small, selected and somewhat heterogeneous group of children followed-up for a relatively short period of time. Acknowledged as a preliminary experience, the data needs to mature prior to declaring it equivalent or superior to current techniques. The widespread acceptance of appendicovesicostomy and bowel-fashioned conduits will now face the challenge of options such as the RPM (Rosito, Pires and Macedo) technique, Perovic's genital skin flap (1) or the continent vesicocutaneous channel by Rackley et al. (video quoted in the Discussion section of the article); all attractive as they appear potentially easier to perform but characterized by a different risk/benefit profile. By virtue of avoiding the use of bowel, problems such as internal hernias, anastomotic leaks, mucous production and intra-peritoneal adhesions may be avoided. The trade-off will likely be a different set of complications particularly related to the use of skin flaps for

intermittent access to bladder drainage. For example, also borrowing from the experience with hypospadias repair, there are specific potential problems that may be of clinical relevance, such as those related to the development of hair follicles within the conduit following puberty. Ultimately, comparative analyses will be needed in order to determine if important long-term outcomes such as stomal stenosis, strictures, leakage and difficulty catheterizing favor one technique over the other. Only time will tell if skin proves to be a suitable alternative to bowel tissue.

The authors are to be congratulated on following a noteworthy pathway for innovative surgical research, by first pursuing feasibility in an animal model prior to proceeding with surgical interventions in children under approval by their Ethics Committee. Overall I find the concept appealing but remain cautiously skeptical. As indicated by the authors, the suggestion that skin based flaps are less morbid, simpler to construct or superior to the alternatives may turn out to be true, but there is paucity of data to categorically support or disprove this assumption. Being the developers of the procedure, they are in prime position to establish prospective clinical research protocols to help us answer many of these questions. As with many other things in medicine, with experience we may discover that patient selection is likely to play an important role. For example, skin-based conduits may not be best for children who undergo concomitant augmentation cystoplasty or with multiple prior surgical interventions with incisions in areas that may compromise the blood supply of the flaps.

I sincerely look forward to a favorable response from the surgical community and hope that after experience with the RPM technique grows we can enjoy the expansion of our surgical options based on the foundations set by this elegant study.

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Use of a Latex Biomembrane for Bladder Augmentation in a Rabbit model: Biocompatibility, Clinical and Histological Outcomes

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ABSTRACT

Purpose: To investigate histological features and biocompatibility of a latex biomembrane for bladder augmentation using a rabbit model.

Material and Methods: After a partial cystectomy, a patch of a non-vulcanized latex biomembrane (2x4 cm) was sewn to the bladder with 5/0 monofilament polydioxanone sulfate in a watertight manner. Groups of 5 animals were sacrificed at 15, 45 and 90 days after surgery and the bladder was removed. The 5-µm preparations obtained from grafted area and normal bladder were stained with hematoxylin-eosin. Immunohistochemical staining was performed with a primary antibody against alpha-actin to assess muscle regeneration.

Results: No death, urinary leakage or graft extrusion occurred in any group. All bladders showed a spherical shape. Macroscopically, after 90 days, the latex biomembrane was not identifiable and the patch was indistinguishable from normal bladder. A bladder stone was found in one animal (6.6%). On the 90th day, histology revealed continuity of transitional epithelium of host bladder tissue on the patch area. At this time, the muscle layers were well organized in a similar fashion to native bladder muscle layers. The inflammatory process was higher on grafted areas when compared to controls: 15 days - $p < 0.0001$, 45 days - $p < 0.001$, and 90 days - $p < 0.01$. The anti alpha-actin immunoexpression peaked at 45 days, when the graft was observed covered by muscle cells.

Conclusion: The latex biomembrane is biocompatible and can be used in models for bladder augmentation in rabbits. It promotes epithelium and muscle regeneration without urinary leakage.

Key words: *bladder; latex; rabbit; smooth muscle; regeneration*
Int Braz J Urol. 2009; 35: 217-26

INTRODUCTION

The worsening quality of life and the loss of upper urinary tract function are consequences of permanent reduction of bladder capacity and compliance, caused by neurogenic or non-neurogenic disorders. Bladder augmentation has the following objectives: reduction of intravesical pressure, improvement of urinary continence and preservation of upper urinary tract function (1). Gastrointestinal segments remains, even today, the most used technique for this purpose. Despite good functional results (2), bladder augmentation with intestinal segments presents disadvantages such as the production of mucus, electrolyte imbalance, development of intestinal and urinary fistula, bladder stones, spontaneous bladder perforation and carcinogenesis (1-3). Auto-augmentation and ureterocystoplasty has emerged as an alternative to override the complications caused by enterocystoplasties, but the first did not elicit long-term consistent results and

the second, depends on the presence of a nonfunctioning kidney unit (4,5).

As non-biodegradable synthetic material for bladder augmentation, such as silicon, polytetrafluoroethylene and polypropylene, has been unsuccessful, the development of biodegradable scaffolds seems to be more appropriate because it would allow the appropriate time to host tissue regeneration with dissolution before a foreign body reaction (6). In recent years, the porcine small intestinal submucosa (SIS) and the bladder acellular matrix graft (BAMG) have been used frequently in experimental studies. They act as biodegradable materials that allow the urothelial and smooth muscle regeneration (7,8). However, the SIS and the BAMG are xenogeneic materials and require advanced technique preparation.

The natural latex biomembrane is extracted from the Hevea brasiliensis. Previous experimental studies have proved that the latex biomembrane is a biodegradable material with easy preparation and handling, encouraging tissue formation and angiogenesis (9,10). No evidence of toxicity or allergenic reaction was found when the latex biomembrane was used to reconstruct the tympanic membrane in humans (11). However, the allergen potential of vulcanized latex is well established in latex glove users and other high-risk groups of patients with different latex exposure (12). This background prompted our interest in enlarging the bladder using this type of latex graft. The aim of the study was to investigate the clinical and histological features as well as the biocompatibility of a latex biomembrane for bladder augmentation in a rabbit model.

MATERIALS AND METHODS

A total of 15 adult male New Zealand rabbits weighing 3.0-3.4 Kg underwent bladder augmentation with the latex biomembrane. This project was approved by the Animal Research Committee of our Institution. Groups of five animals were sacrificed at 15 (group A), 45 (group B) and 90 (group C) days after grafting. As controls, in each rabbit we excised a bladder full thickness fragment distant from the grafted area.

Membrane Preparation

Matrix preparation followed the technique published previously (10). Briefly, the latex extracted from the Hevea brasiliensis tree was poured as a thin layer on Petri dishes and dried in an oven at 60ºC for 20 minutes in order to promote the polymerization of latex's constituents. The latex membranes so obtained were immersed in a 0.1% solution of poly-L-lysine hydrobromide (MW 70-140 kD, Sigma) for 24h at room temperature. Then, the membranes were placed into a dry-heat oven at 60ºC for 2 hours, packed and sterilized in ethylene oxide.

Surgical Technique

The animals were anesthetized by intramuscular injection of ketamine (35 mg/kg) and xylazin (5 mg/kg). A partial cystectomy (4.0 cm^2 - 2.0 x 2.0 cm), corresponding to nearly 15% of bladder size, was performed through a median laparotomy. A patch of 2.0 x 2.0 cm of the latex biomembrane was grafted onto the remaining host bladder with a continuous suture of 5/0 monofilament absorbable polydioxanone sulfate. Four marking stitches of 5/0 polypropylene were placed outside the bladder wall near the corners of the patch. Perivesical fat was fixed over the bladder wall to cover the graft.

Follow-up

Enrofloxacyn (9 mg/Kg) was given subcutaneous to all animals daily for 2 postoperative days. The clinical condition of all animals was evaluated daily from surgery until the sacrifice. The sacrifice was carried out with an intravenous injection of pentobarbital (60 mg/Kg). A macroscopic inspection was then performed before bladder removal. A silk ligature was placed around the urethra, samples for immunohistochemistry were taken and the bladder was filled in with 10% formalin and then immersed in the same solution.

Histology and Immunohistochemistry

Formalin fixed specimens from the grafted and control areas of the bladder were embedded in paraffin. Sections of 5 μm were cut and stained with hematoxylin and eosin in order to evaluate the amount of inflammatory cells in the graft.

For immunohistochemistry, samples from grafted and control areas were immediately fixed for 24h in ice-cold 0.1 M PBS, ph 7.4, containing 4% paraformaldehyde, followed for cryoprotection in 15% of sucrose for 4h and 30% sucrose overnight at 4°C. Longitudinal sections (3 μm) of samples were incubated with 3% H2O2 and Pierce solution to block endogenous peroxidase and biotin, respectively. Sections were subsequently incubated with primary antibodies against anti-smooth muscle alpha-actin (1:80 dilution, clone RBC2/1B6, Novocastra®) and with biotin-conjugated secondary anti-rabbit antibody (1:1000; Vector Laboratories Inc., Burlingame, USA) and streptavidin-conjugated peroxidase (Vecstatin Abc kit, Vector Laboratories Inc.). Color was developed by the addition of DAB (Sigma Chemical, St. Louis, USA). To evaluate the background reaction, procedures were also performed in sections incubated only with the secondary antibodies (indirect technique) or in the absence of antibodies (direct technique). The number of cell with positive staining for alpha-actin was estimated by using a camera (Axio Cam, Zeiss, Germany) and the program Axiovision 4.6 (Zeiss, Germany).

In histological / immunohistochemical evaluation, 10 microscope fields were examined. Cells were counted at a 400X magnification by two different pathologists in a blind manner. The semi-quantitative analysis was determined and expressed as a percentage of inflammatory cells and cells labeled with anti-smooth muscle alpha-actin, as follows: Score 0: 0-5%, Score I: 5-25%, Score II: 25-50%, Score III: 50-75% and Score IV: > 75%.

Statistical Analysis

Data are provided as medians and range. The comparisons between the treated and controls areas were analyzed by the Wilcoxon test. The relationships between groups were analyzed with analysis of variance (Kruskal-Wallis test), followed by the Dunn's test to compare individual pairings. Statistical analysis was performed using the GraphPad Prism 4.03 program (San Diego, CA, USA) and p values < 0.05 were considered statistically significant.

RESULTS

Macroscopic Evaluation

All rabbits were able to void spontaneously after the operation and no animal exhibited urinary leakage. All bladders had a spherical shape.

On the 15th postoperative day, blood vessels were visible around the grafted area. After a longitudinal incision of the bladder, the presence of the latex matrix was easily identified since it was almost intact.

On the 45th day after surgery, the graft was almost entirely integrated to the host tissue of the native bladder. Bladder wall was thicker, mainly around the latex membrane. One bladder stone (1.5 x 2.0 cm) was observed in one rabbit (6.6%).

After 90 days from surgery, there was a decrease on bladder wall hypertrophy and the graft was indistinguishable from the normal host bladder at inner and outer surfaces. There was blood vessel reduction around the grafted area (Figure-1).

Microscopic Evaluation

On the 15th postoperative day, the luminal surface of the latex matrix was still uncovered by the urothelium. Fibrovascular reaction was present, with rare fibroblasts and a moderate amount of inflammatory cells, mainly macrophages. Forty-five days after surgery there was a diffuse epithelial and smooth muscle hyperplasia on the graft. At 90 days, there was a reduction on epithelial and muscle hyperplasia, and the urothelium was similar to the native bladder (Figure-2). At this time, the smooth muscle layers were well organized and in a similar direction in comparison to native bladder muscle layers.

Inflammatory Response

Significant inflammatory cells were not observed in the controls (score 0). The inflammatory process was higher 15 days after the procedure and decreased gradually from the time of grafting, tending to normalization at 90 days. This occurred despite the significant difference between grafted and non-grafted areas in all groups (Table-1).

The neutrophils and mononuclear cells were the main component of the widespread inflammatory process in the patch from group A, but inflammation

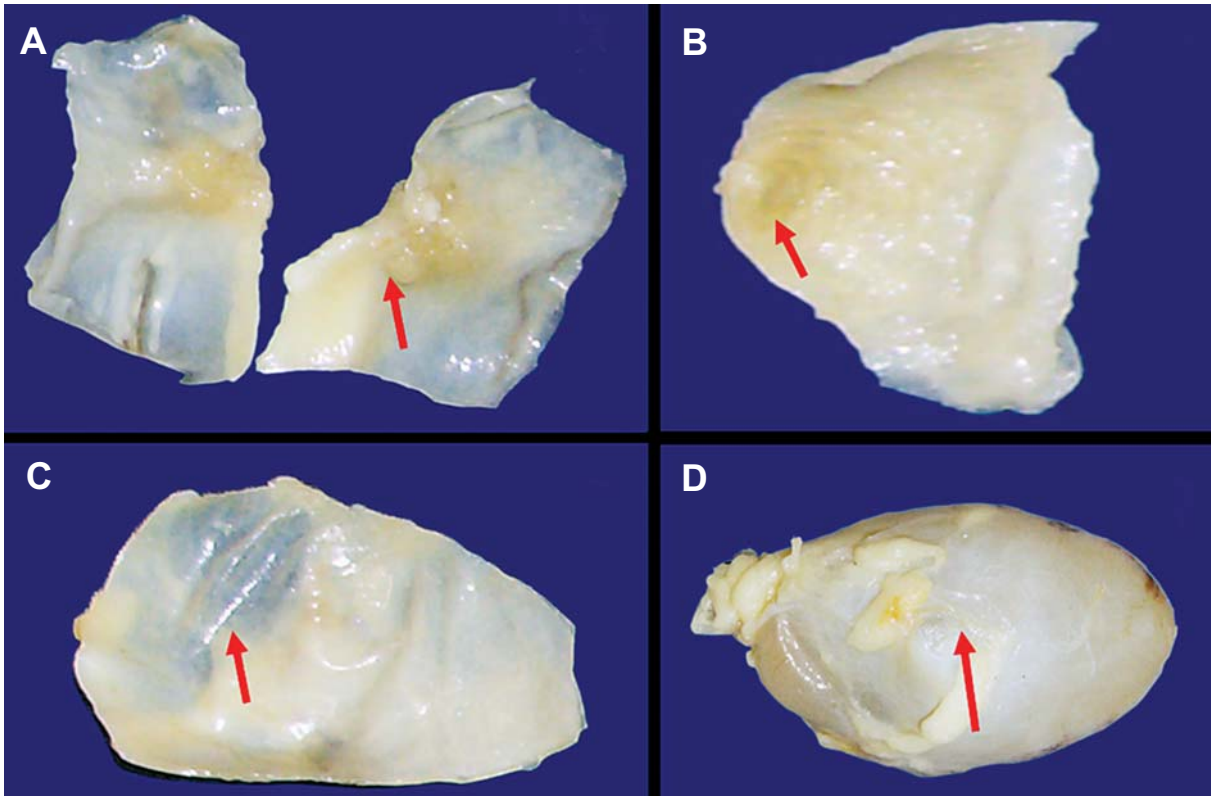

Figure 1 *– Macroscopic evaluation of the latex biomembrane. A) Presence of the membrane 15 days after surgery. B) Thick bladder wall at 45 days. C) and D) Incorporation of the latex membrane (interior) and spherical architecture (exterior) after 3 months.*

decreased with the time of follow-up being restricted around the remaining latex membrane in group C (Figure-3).

Smooth Muscle Layer Regeneration

The infiltration of alpha-actin-positive cells started from the border toward the center of the graft. During the first 15 days (Group A), the bladder smooth cell regeneration had began poorly and did not exhibit spatial organization, mainly near the anastomosis area. The expression of alpha-actin positive cells peaked at 45 days (Group B) after surgery, and then, slowly decreased. By the 90th post-surgical day (Group C), the smooth muscle cells were well developed and oriented, however it was difficult to distinguish the junction between the graft area and host bladder muscle (Figure-4).

The expression of the alpha-actin varied significantly according to the time elapsed ($p = 0.001$) (Kruskal-Wallis' test). Higher expression was detected in grafted area in animals from group B (45th day) that was statistically different in comparison with groups A (15th day) and C (90th day) ($p = 0.001$). When compared to controls the expression was significantly higher in groups B and C and was similar in group A. (Wilcoxon paired test). There was no change in the expression of alpha-actin in non-grafted areas with time (Table-1).

COMMENTS

The ideal material for bladder augmentation should allow the progressive growth of all components of the normal bladder wall, preserving their mechanical and functional properties (7,8,13). Probst et al. (8) showed that bladder augmentation in rats with BAMG is associated with a high mortality rate

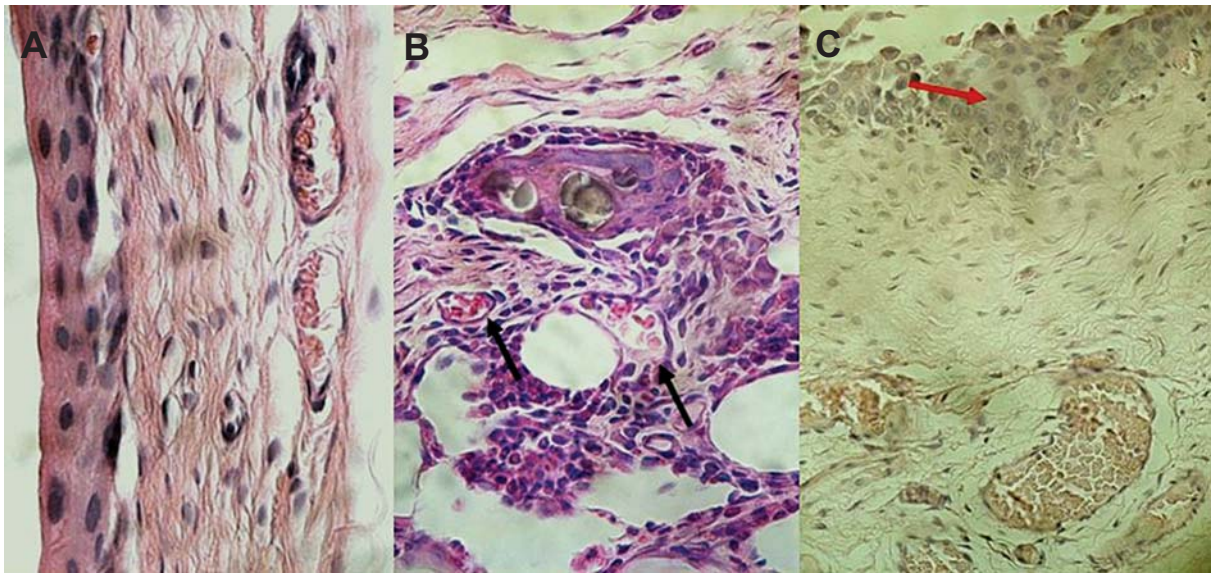

Figure 2 – *A) Non-grafted area (controls). B) Blood vessels 15 days after grafting (black arrows). C) Urothelial layer 90 days after surgery (red arrow). HE, X400.*

(32%) due to urinary leakage and/or bladder neck obstruction. However, in the surviving rats, the graft was progressively infiltrated by vessels and smooth muscle cells of the host and the mucosal lining was complete within 10 days. The ingrowth was complete after 8 weeks, except for neural regeneration, which was only partial. At 12 weeks, the bladder wall muscle structure in the graft was so well developed that it was difficult to delineate the junction between host bladder and BAMG. These authors concluded that BAMG appears to serve as a framework of collagen and elastin for the ingrowths of all bladder wall components. The high mortality rate caused by urinary leakage in the model of bladder augmentation in rats with BAMG has also been reported elsewhere (13). Ayyildiz et al. (7) reported that SIS seems to be a viable alternative to the use of intestine in bladder augmentation in rabbits since at the end of 12 months, the long-term

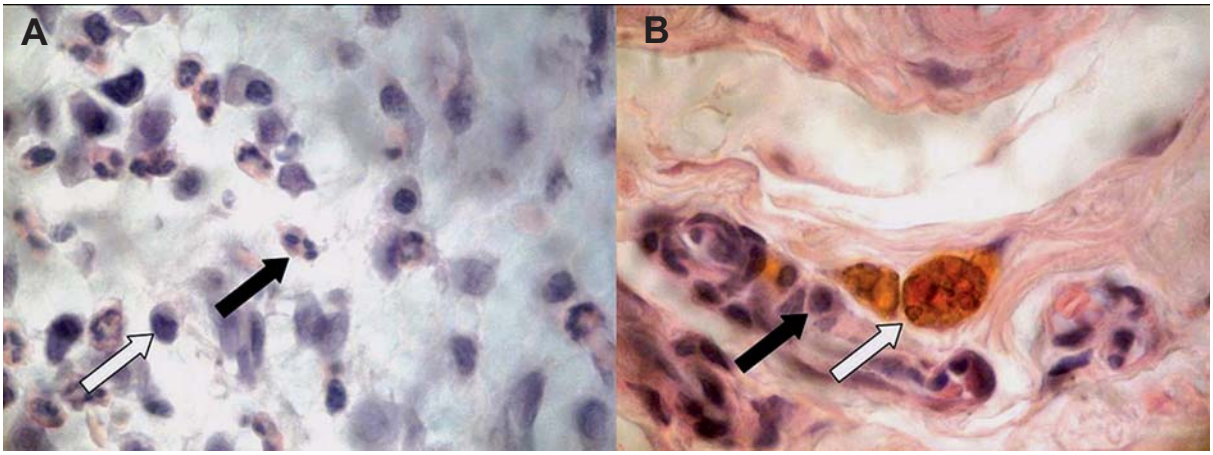

Figure 3 – *A) Inflammatory cells in the grafted area 15 days after surgery - neutrophil (black arrow) and mononuclear leukocyte (white arrow). B) Inflammatory response - lymphocytes (black arrow) around the remaining latex membrane (white arrow) after 90 days.*

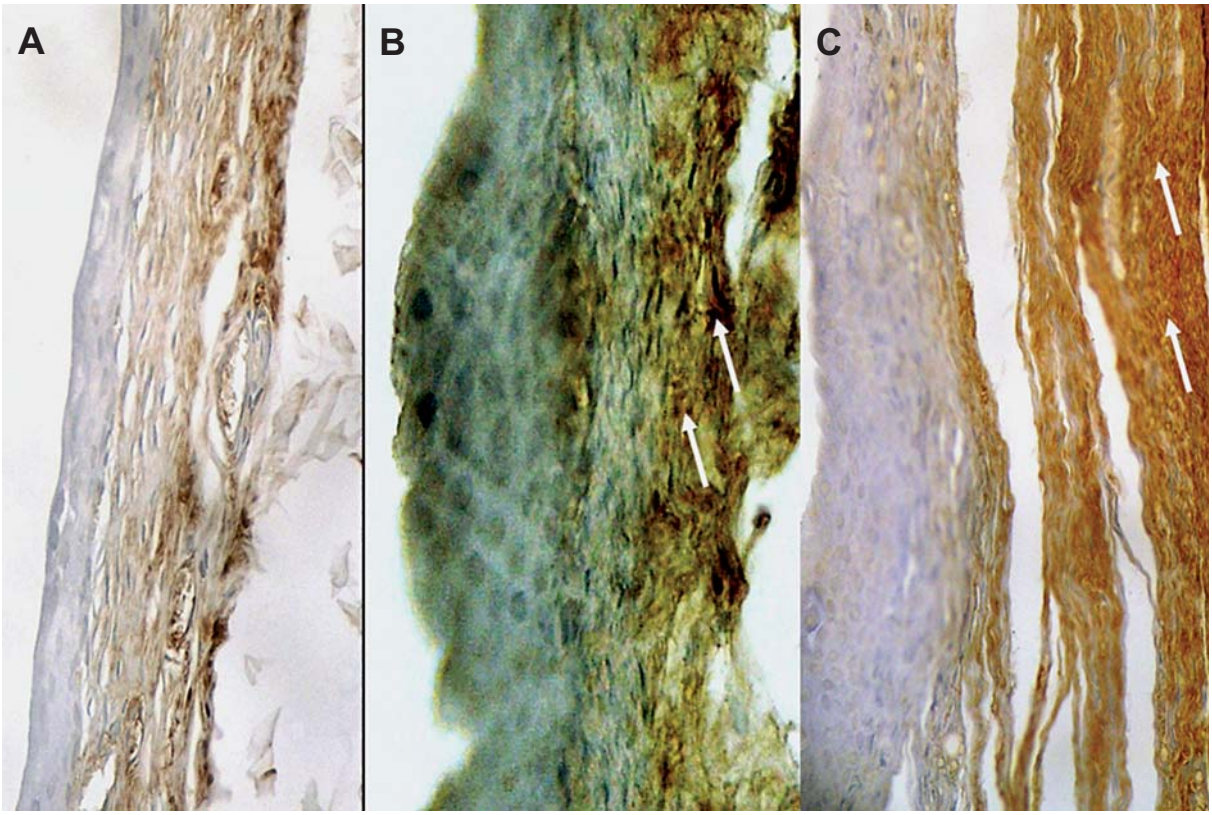

Figure 4 – *Changes in alpha-actin expression over time. A) Muscle layer of non-grafted area. B) Hyperplasia of smooth muscle cells growing into the latex biomembrane 45 days after surgery; note the high expression of alpha-actin (stained in brown - white arrows). C) Reduction of alpha-actin-positive expression and muscular cells with a lesser degree of hyperplasia 3 months after surgery.*

Table 1 – *Inflammatory response and alpha-actin immunoexpression according to the groups at different times of evaluation. Data expressed as medians and ranges.*

	Control	Experimental	p Value *
Inflammatory Response			
15th day	0	3 (3-4)	< 0.0001
45th day	0	2 (1-2)	< 0.001
90th day	0	1 (1-2)	< 0.01
Alpha-actin			
15th day	1	1 (1-2)	ns
45th day	1	3 (2-3)	< 0.001
90th day	1	2 (1-2)	0.02

*Numbers represent score; * Wilcoxon paired test; ns = not significant.*

histological features of bladder augmentation was indistinguishable from original bladder. The rabbit model is suitable for bladder tissue engineering studies, but bladder augmentation with SIS or collagen-based biomatrix exhibits a high rate (37%) of stone formation and/or encrustation of foreign body material (14).

Our data show for the first time that latex biomembrane used for bladder augmentation in rabbits allows a progressive ingrowth of all components of the normal bladder wall without postoperative urinary leakage and a low rate of stone formation. After 3 months, the smooth muscle cells were well developed and oriented, and were difficult to delineate the junction between the grafted area and host bladder muscle. It also seems that this biodegradable material offers the advantage to reduce the rate of stone formation or encrustation (6.6%) in comparison with SIS, collagen-based biomatrix and bowel segments.

The inflammatory process in bladder augmentation with collagen-based biomatrix may be secondary to early congestion of the grafts as well as to stimuli caused by the graft components (15). This reaction was stronger in the first 2 weeks following the surgery, but thereafter its intensity reduces progressively. The inflammatory process must be temporary and not lead to graft rejection (8). The vigorous inflammatory response caused by grafted extracellular matrix is restrict to a TH2 lymphocytes immune response, which results in tissue remodeling rather than tissue destruction or rejection (16). Our data with latex biomembrane showed that the inflammatory reaction was more intense on the 15th postoperative day and decreased significantly later on, which may be regarded as an evidence of no rejection. Previous reports on production of inflammation cytokines induced by latex biomembrane in vitro showed enhancement of production of interleukin-10 and reduction of interferon Y, which suggest that such material elicits an immune response restricted to TH2 lymphocytes (17). It is relevant to stress that during latex biomembrane preparation, one must preserve the native conformation of latex proteins by avoiding temperatures higher than 60ºC and hence the latex vulcanization, otherwise the inflammatory response changes from a tissue repair type toward a rejection type, as shown previously by electron microscopy (9,18).

The exact origin of smooth muscle cells (SMC) in the bladder grafts remains unclear. Some authors suggest a major role for pluripotential stem cells in the graft cellular regeneration (19,20). On the other hand, other authors have demonstrated that muscle layer regeneration occurs by migration of dedifferentiated bladder SMC from the matrix-bladder junction (15). Previous experimental studies with the latex biomembrane have shown that it allows the ingrowths of epithelial, submucosal glands and muscular cells of canine esophagus (9). The results of our study suggest that the muscle layer regeneration occurs from the host bladder since alpha-actin was first observed in this area. Bladder augmentation with other extracellular matrix graft showed that the expression of alpha-actin was first visualized on day 4 after the procedure, peaked at day 10 and then decreased. Expression increased again gradually after 3 to 4 weeks and progressed for 12 weeks (14). The early peak of alpha-actin expression was interpreted most likely as a consequence of artifacts caused by the higher number of cells in the matrix rather than the real expression of muscle cells in the matrix. Other studies showed a progressive expression of alpha-actin from 15% in the first 2 weeks to 36% in the 12th week, at a time when muscle layer was well developed and oriented (8). The current study demonstrated that the alpha-actin expression was higher 45 days after surgery and decreased thereafter. At the end of the experiment, muscle layer was well organized, similar to the host tissue. These findings support the idea that latex biomembrane can be used as a matrix in experimental studies of bladder augmentation because it is well tolerated and promotes adequate smooth muscle regeneration.

CONCLUSION

This study demonstrates the biocompatibility of the latex biomembrane as a matrix for bladder augmentation in rabbits. The matrix promotes epithelium and muscle regeneration without urinary leakage. More detailed investigations on its functional properties are warranted in the future.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

I have read an interesting paper entitled, "Use of a Latex biomembrane to bladder augmentation in rabbits: biocompatibility, clinical and histological outcomes" prepared by Dr. Domingos and colleagues. Bladder tissue engineering is a developing field of regenerative medicine regardless the objective difficulties of in vitro creation of functional bladder wall. Bladder wall regeneration by means of tissue engineering techniques depends on several factors, i.e.: cells, proper scaffold, nutrition and stimulus supply within the host organism. This paper is dedicated to scaffold. The optimal conditions for the proliferation of bladder cells, their terminal differentiation and influence on neo-tissue remodeling were shown to be a desired behavior of both transplanted and host cells. A good scaffold can help to achieve this difficult task, by promotion of mentioned above processes. It was proved that even decellularized animal or human scaffolds were not ideal. The deposition of dense connective tissue and scarring are often observed during healing of tissue-engineered bladder wall. The failure of regeneration can be evoked by allo- or xenogenic cellular remnants within the biological scaffold, urine leakage, etc. Poorly compliant bladder is a result of these unwanted events. Bladder regeneration is much more complicated in a disease condition. The most current experimental works are performed on healthy bladders. There is still a need to create a low immunogenic, high adhesive and biocompatible scaffold for bladder tissue engineering. Dr. Domingos and colleagues are working in this field. They show that even latex can be prepared in such way to be atoxic to bladder cells and promoted in vivo regeneration. They presented bladder wall regeneration induced by latex modified biomaterial within the animal model. It should be emphasized that scaffold has to be a biological niche for differentiated cells and their stem (undifferentiated) counterparts during in vivo regeneration. It seems that the role of scaffold during the regeneration process is equal to cellular compartment, so I have found this work important. This paper is a very good "background" for the future experiments with the cell-seeded matrices performed on healthy and disease affected bladders.

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EDITORIAL COMMENT

Many different materials have been investigated for use as scaffolds in tissue engineering. In bladder augmentation models these materials have included collagen, synthetic polyesters such as polyglycolic acid, bladder acellular matrix grafts, and porcine small intestine submucosa. The authors present their initial histological findings using a latex biomembrane scaffold for bladder augmentation in rabbits. Multiple groups from the University of Sao Paulo have shown that the latex biomembrane allows healing in the esophagus (1), the mastoid and dental alveolar bones (2,3) and ulcerated skin (4). In this manuscript, the authors similarly observed progressive smooth muscle growth at the bladder graft site and concluded that further functional studies of the latex biomembrane in the bladder are warranted.

Several concerns will need to be addressed in order to determine if the latex biomembrane bladder augmentation is applicable to human patients. Prior in vitro studies have shown than latex is more

cytotoxic to cultured bladder smooth muscle cells compared to other traditional biomaterials (4). More importantly, a large percentage of patients requiring bladder augmentation are children with spina bifida who have a high risk of latex allergy. Nonetheless, the authors should be commended for their initial work using a novel scaffolding material in bladder augmentation.

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International Braz J Urol Vol. 35 (2): 227, March - April, 2009

Re: In Vitro Evidence for a New Therapeutic Approach in Renal Cell Carcinoma

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Int Braz J Urol, 34: 492-502, 2008

To the Editor,

I hereby wish to make the following statement regarding the above-mentioned article. As the head of the laboratory at Istituto Superiore di Sanità (Italian National Institute of Health), in which the corresponding author, Dr. Carmine Pittoggi, has been working until November 2007, I declare that no data on renal carcinoma-derived cells have ever been produced under my supervision or with my knowledge during the time that Dr. Pittoggi has spent in my laboratory.

Whether Dr. Pittoggi has done the experiments in my own lab without my knowledge, or whether he has done the work elsewhere on other premises, I cannot be and do not want to be senior author of a work which I have not supervised or approved of, and for which I do not even know how, when or where the data was produced. I therefore request officially that my name be dissociated from the publication.

The signature besides my name in the submission letter written by Dr. Carmine Pittoggi and accompanying the original manuscript is not my own. I am taking legal steps to inform officially the legal Office Istituto Superiore di Sanità, to which a copy of this letter is being forwarded, as well as the Director of Personnel and the President of the National Institute of Health, that my signature has been falsified in an official document.

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International Braz J Urol
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UROLOGICAL SURVEY

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STONE DISEASE

Combined retrograde flexible ureteroscopic lithotripsy with holmium YAG laser for renal calculi associated with ipsilateral ureteral stones

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Purpose: The purpose of this study was to evaluate the effectiveness of combined ureteroscopic holmium YAG lithotripsy for renal calculi associated with ipsilateral ureteral stones.
Materials and Methods: Between August 2002 and March 2007, retrograde flexible ureteroscopic stone treatment was attempted in 351 cases. Indication for treatment was concurrent symptomatic ureteral stones in 63 patients (group I). Additional operative time and perioperative complication rates were compared to a group of 39 patients submitted to ureteroscopic treatment for ureteral calculi exclusively (group II).
Results: Mean ureteral stone size was 8.0 ± 2.6 mm and 8.1 ± 3.4 mm for groups I and II, respectively. Mean operative time for group I was 67.9 ± 29.5 minutes and for group 2 was 49.3 ± 13.2 minutes ($p < 0.001$). Flexible ureteroscopic therapy for renal calculi increased 18 minutes in the mean operative time. The overall complication rate was 3.1% and 2.5% for groups I and II, respectively ($p = 0.87$). Mean renal stone size was 10.7 ± 6.4 mm, overall stone free rate in group I was 81%. However, considering only patients with renal stones smaller than 15 mm, the stone free rate was 88%. Successful treatment occurred in 81% of patients presenting lower pole stones, but only 76% of patients with multiple renal stones became stone free. As expected, stone free rate showed a significant negative correlation with renal stone size ($p = 0.03$; $r = -0.36$). Logistic regression model indicated an independent association of renal stones smaller than 15 mm and stone free rate (OR = 13.5; $p = 0.01$).
Conclusion: Combined ureteroscopic treatment for ureteral and ipsilateral renal calculi is a safe and attractive option for patients presenting for symptomatic ureteral stone and ipsilateral renal calculi smaller than 15 mm.

Editorial Comment

The authors are to be commended for the high stone-free rate obtained with the stringent criteria based on CT scan imaging. One might consider that it could be difficult to standardize instrumentation and technique across three continents and across a 5-year time period - this may impact the interpretation of results especially if a larger bulk of the flexible ureteroscopies were conducted in the later portion of the study period when the authors had more experience and better instrumentation. It would be helpful for the authors to define their criteria for using a ureteral access sheath - it is our practice to use it routinely during intrarenal stone extraction to improve stone frees rates and minimizes the risk of ureteral injury.

The authors importantly define the upper limit of stone size to tackle ureteroscopically - 15 mm. Beyond this size one must inform patients of the risk of requiring staged ureteroscopies to render stone-free. Another important consideration is that all patients were stented after the surgery. As 60% of these patients had distal ureteral calculi, they could have been offered the alternative of no stent if intrarenal calculi were not treated at the same setting. Often patients who have had significant stent discomfort in the past will elect to leave the intrarenal stone untreated so as to avoid the ureteral stent.

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Percutaneous versus transurethral cystolithotripsy

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J Endourol. 2009; 23: 237-41

Purpose: To compare transurethral cystolithotripsy (TUCL) and percutaneous cystolithotripsy (PCCL) modalities performed during simultaneous transurethral resection of the prostate (TURP) in patients with prostate hyperplasia and large bladder stones.
Patients and Methods: Sixty-three patients with prostate volume > 40 cc and aggregate stone size > 2.5 cm were enrolled in the study between August 2003 and February 2007. TUCL (n = 38) or PCCL (n = 25) procedures were performed during simultaneous TURP. In the TUCL group, the stones were removed after fragmentation through a 23F cystolithotripter with pneumatic lithotripsy. This was followed by TURP, performed with a 26F continuous-flow resectoscope. In the PCCL group, the stones were removed through a suprapubic 30F Amplatz sheath after fragmentation. TURP was then performed with the suprapubic sheath providing continuous drainage.
Results: Mean age and prostate volumes of the groups were similar. Mean aggregate stone sizes were significantly larger in the PCCL group. The operative time for stone removal was significantly less in the PCCL group while time needed for TURP was statistically similar in the two groups. In the TUCL group, three patients had residual stones necessitating repeated TUCL and urethral stricture developed in three patients.
Conclusion: The smaller caliber of the working channel during TUCL, compared with PCCL, necessitates disintegration of the stones into smaller fragments. This elongates the duration of the intervention and results in increased urethral and bladder trauma. Combined TURP and PCCL is a safer, more effective, and much faster alternative to combined TURP and TUCL in patients with large bladder stones and prostate hyperplasia.

Editorial Comment

The study is limited in its retrospective nature, but provides important support for the empiric approach utilized by the authors. It is clear that transurethral approach carries a higher risk of urethral stricture - this may be related to the duration of instrumentation during stone extraction or it may be related to the size and duration of post-operative catheterization. The authors emphasize the importance of stone extraction prior to TURP as bleeding from the prostatic fossa may obscure the identification of residual stone. The authors also emphasize the importance of leaving the Amplatz sheath in place during the TURP as premature removal of this may lead to extraperitoneal extravasation of irrigation fluid. Another advantage of a percutaneous approach not mentioned by the investigators would be the use of an ultrasonic lithotripter through a rigid nephroscope as a more efficient means of stone clearance. Lastly, it is important to note that these recommendations are specific for men - though less common, larger stones in women can be effectively addressed cystoscopically with a rigid nephroscope and ultrasonic lithotripter.

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ENDOUROLOGY & LAPAROSCOPY

Comparison of different extraction sites used during laparoscopic radical nephrectomy

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J Urol. 2009; 181: 1565-70

Purpose: Laparoscopic radical nephrectomy is commonly performed for renal tumors that are not amenable to nephron sparing treatment. A number of techniques for intact specimen extraction are used. The development of incisional hernias from the extraction site is a known but infrequent delayed complication. We analyzed different extraction sites and risk factors for such hernias.
Materials and Methods: We retrospectively analyzed a cohort of patients undergoing laparoscopic radical nephrectomy with intact specimen extraction through 3 sites. Patients and operation specific parameters were included with particular attention to factors predisposing patients to incisional hernia, including chronic obstructive pulmonary disease, diabetes mellitus, chronic steroid use and a high body mass index.
Results: A total of 181 nephrectomies were performed in 175 patients and 175 kidneys (96.7%) had malignancy. Mean tumor size was 4.9 cm. Mean followup was 28.8 months. Extraction was done from a lower quadrant site in 55 patients (31.4%), from the umbilical site in 58 (33.2%) and from a paramedian site in 62 (35.4%). Patients with paramedian and lower quadrant extraction sites were older ($p = 0.016$), and had a higher body mass index ($p = 0.001$) and greater specimen weight ($p = 0.003$). In 4 patients an incisional hernia developed. An incisional hernia was significantly associated with the paramedian extraction site ($p = 0.015$).
Conclusions: Incisional hernias may occur as a delayed complication of laparoscopic radical nephrectomy. This complication most commonly develops at the extraction site. In patients with a high body mass index using a paramedian extraction site is a significant risk factor for incisional hernia formation.

Editorial Comment

Laparoscopic radical nephrectomy has evolved and questions such as intact organ extraction versus morcellation were answered by different investigators recommending intact extraction for different reasons. Unfortunately, larger extraction sites may cause incisional hernia. The authors have demonstrated that when patients are obese the optimal site for extraction is the paramedian site since it may decrease the chance for incisional hernia after extraction.

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Laparoscopic management of endopelvic etiologies of pudendal pain in 134 consecutive patients

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Purpose: The feasibility of the laparoscopic transperitoneal approach to the pelvic somatic nerves was determined for the diagnosis and treatment of anogenital pain caused by pudendal and/or sacral nerve root lesions.

Materials and Methods: The records of 134 consecutive patients who underwent laparoscopy for refractory anogenital pain were retrospectively reviewed. All neurosurgical procedures, such as neurolysis/decompression of the pudendal nerve and the sacral nerve roots or neuroelectrode implantation to the sacral plexus for postoperative neuromodulation, were done via the laparoscopic transperitoneal approach to the pelvic nerves. Results: A total of 18 patients had Alcock's canal syndrome and decompression was successful in 15. Due to failed decompression 3 patients underwent secondary sacral laparoscopic neuroprosthesis implantation with a decrease of at least 50% on the pain visual analog scale. Sacral plexus lesions or radiculopathies, most commonly postoperative lesions and retroperitoneal endometriosis, were found in 109 patients who underwent laparoscopic neurolysis of the sacral plexus. The final outcome depended on the etiology. Of patients with postoperative nerve damage 62% had a decrease in the mean +/- SD preoperative visual analog scale score of from 8.9 +/- 2.9 (range 7 to 10) to 2.4 +/- 2.3 points (range 0 to 4) at the time of article submission at a mean followup of 17 months (range 3 to 39). Because of failed decompression, 8 patients underwent secondary sacral laparoscopic neuroprosthesis implantation and a decrease in the pain visual analog scale score was achieved in 5. Of patients with an endometriosis lesion of the sacral plexus 78% had a decrease in the mean preoperative visual analog scale score of 8.7 +/- 1.9 (range 8 to 10) to 1.1 +/- 0.7 points (range 0 to 2) at the time of article submission at a mean followup of 21 months (range 2 to 42). All 6 patients with vascular entrapment of pelvic nerves achieved complete relief. The last 7 patients underwent primary sacral laparoscopic neuroprosthesis implantation with at least a 50% decrease in the pain visual analog scale score in 4.
Conclusions: Our findings emphasize that in patients with seemingly inexplicable anogenital pain, especially after failed treatment for Alcock's canal syndrome, laparoscopic exploration of the pelvic nerves must be done for further diagnosis and therapy before prematurely labeling the patients as refractory to treatment.

Editorial Comment

Laparoscopic minimally invasive approach has been applied in Urology for benign, oncological diseases, reconstructive surgery; but this novel approach to manage endopelvic etiologies of pudendal pain is a pioneer approach to a complex urogynecological problem.

The author describe a protocol that when followed seemed to successfully deal with the complex pelvic pain disease.

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IMAGING

Renal cell carcinoma: dynamic contrast-enhanced MR imaging for differentiation of tumor subtypes--correlation with pathologic findings

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Purpose: To retrospectively evaluate whether the enhancement patterns of pathologically proved clear cell, papillary, and chromophobe renal cell carcinomas (RCCs) measured on clinical dynamic contrast agent-enhanced magnetic resonance (MR) images permit accurate diagnosis of RCC subtype.

Materials and Methods: This study was Institutional Review Board approved and HIPAA compliant; informed consent was waived. One hundred twelve patients (76 men, 36 women; age range, 25-88 years; mean age, 58.1 years) underwent MR imaging of 113 renal masses (mean diameter, 5.4 cm) with pathologic diagnoses of clear cell (n = 75), papillary (n = 28), or chromophobe (n = 10) RCC. A 1.5-T clinical MR protocol was used before and after (corticomedullary and nephrographic phases) intravenous administration of contrast agent. Region-of-interest measurements within tumor and uninvolved renal cortex were used to calculate percentage signal intensity change and tumor-to-cortex enhancement index. Subtype groups were compared by using linear mixed-effects models. Receiver operating characteristic (ROC) curve analysis was performed for the comparison of clear cell and papillary RCCs.
Results: On both the corticomedullary and nephrographic phase images, clear cell RCCs showed greater signal intensity change (205.6% and 247.1%, respectively) than did papillary RCCs (32.1% and 96.6%, respectively) ($P < .001$). Chromophobe RCCs showed intermediate change (109.9% and 192.5%, respectively). The tumor-to-cortex enhancement indexes at corticomedullary and nephrographic phases were largest for clear cell RCCs (1.4 and 1.2, respectively), smallest for papillary RCCs (0.2 and 0.4, respectively), and intermediate for chromophobe RCCs (0.6 and 0.8, respectively). Signal intensity changes on corticomedullary phase images were the most effective parameter for distinguishing clear cell and papillary RCC (area under ROC curve, 0.99); a threshold value of 84% permitted distinction with 93% sensitivity and 96% specificity.
Conclusion: Clear cell, papillary, and chromophobe RCCs demonstrate different patterns of enhancement on two-time point clinical dynamic contrast-enhanced MR images, allowing their differentiation with high sensitivity and specificity.

Editorial Comment

Each subtype of RCC is associated with a different prognosis and tumor behavior. If possible, preoperative characterization of RCC subtypes would influence the degree of preoperative evaluation and the determination of the appropriate extent of surgery (1-3). For example a patient with a subtype that tends to not metastasize or recur, such as the chromophobe, may not need to undergo a complex metastasis survey and unnecessarily wide resection may be avoided, thereby, decreasing postoperative morbidity and mortality (3). For this reason, adequate preoperative characterization of the RCC subtype has been attempted utilizing contrast enhanced CT studies (2,3). On multiphase contrast enhanced the clear cell (70.3%) and papillary (69.2%) subtypes tended to show heterogeneous or predominantly peripheral enhancement, whereas the chromophobe subtype (75%) usually showed homogeneous enhancement.

The authors of this excellent original study found in a study of 112 patients that clear cell, papillary, and chromophobe renal cell carcinoma demonstrated different enhancement patterns when assessed with 3D T1-weighted spoiled gradient-echo sequences before and after (corticomedullary and nephrographic phases) contrast material administration. It is interesting to note that differently from contrast enhanced CT studies, the best results of this dynamic contrast enhanced MR technique was accomplished using analysis of signal intensity in the corticomedullary phase.

As the author mentioned in the text, if their results are confirmed with a larger prospective study, this method would provide equivalent accuracy to that reported for percutaneous biopsy. Probably both techniques will be used together in the preoperative evaluation of renal mass since percutaneous biopsy is the only technique that provides Fuhrman grade immunohistochemical stain.

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Correlation of MR imaging and MR spectroscopic imaging findings with Ki-67, phospho-Akt, and androgen receptor expression in prostate cancer

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Purpose: To retrospectively assess whether magnetic resonance (MR) imaging and MR spectroscopic imaging and selected molecular markers correlate with each other and with clinically insignificant and significant prostate cancer (PCa), as defined at surgical pathologic analysis.
Materials and Methods: The institutional review board approved this HIPAA-compliant study and waived informed consent. Eighty-nine men (mean age, 63 years; range, 46-79 years) with biopsy-proved PCa underwent combined endorectal MR imaging and MR spectroscopic imaging before radical prostatectomy. Suspicion of clinically insignificant PCa was retrospectively and separately recorded for MR imaging and combined MR imaging and MR spectroscopic imaging by using a scale of 0-3. Clinically insignificant PCa was pathologically defined as organ-confined cancer of 0.5 cm(3) or less without poorly differentiated elements. Prostatectomy specimens underwent immunohistochemical analysis for three molecular markers: Ki-67, phospho-Akt (pAkt), and androgen receptor (AR). To examine differences in marker levels for clinically insignificant and significant cancer, a Wilcoxon rank sum test was used. To examine correlations between marker levels and MR imaging or combined MR imaging and MR spectroscopic imaging scores, the Spearman correlation was used.
Results: Twenty-one (24%) patients had clinically insignificant and 68 (76%) had clinically significant PCa at surgical pathologic review. All markers were significantly correlated with MR imaging and combined MR imaging and MR spectroscopic imaging findings (all correlation coefficients > 0.5). In differentiating clinically insignificant from clinically significant PCa, areas under the receiver operating characteristic curves for Ki-67, AR, pAkt, MR imaging, and combined MR imaging and MR spectroscopic imaging were 0.75, 0.78, 0.80, 0.85, and 0.91, respectively.
Conclusion: The use of pretreatment MR imaging or combined MR imaging and MR spectroscopic imaging and molecular marker analyses of biopsy samples could facilitate better treatment selection. Supplemental material: http://radiology.rsnajnls.org/cgi/content/full/250/3/803/DC1.

Editorial Comment

Insignificant prostate cancer is defined as cancer found on biopsy (T1c), with PSAD < 0.15 ng/mL, Gleason score 6 or lower, or no more than 2 cores with cancer or greater than 50% involvement of any core. As we know insignificant prostate cancer is better defined as low-volume, low-grade tumor since around 10 % of this lesions may present with extra-prostatic extension on radical prostatectomy (1). In this very interesting

manuscript, the authors reported a frequency of 24% of patients with clinically insignificant prostate cancer at radical prostatectomy. Although with some controversy (2), the same group of authors has been shown recently that a nomogram that incorporates MRI and MRSI was more accurate than clinical nomograms (clinical stage, PSA level, biopsy data) in order to predict clinically insignificant prostate cancer (3).

In a study of 89 men with biopsy-proven prostate cancer, the authors demonstrated that combined MRI and MRSI findings and three specific biologic markers that are important in proliferation, apoptosis, and cell survival (Ki-67, phospho-Akt, and androgen receptor AR values) correlated with each other and with clinically insignificant and significant prostate cancer defined at pathologic examination of prostatectomy specimens.

We agree with the authors that if a prospective study confirms their results it may represent the beginning of a new era. An era of integration of pretreatment conventional and functional MR imaging of the prostate with histopathological and specific biologic markers analyses of biopsy specimens. In the near future, this integration probably will allow better treatment selection and thus better outcome for patients with prostate cancer.

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PATHOLOGY

TMPRSS2-ERG gene fusions in "minimal" prostatic adenocarcinoma

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Mod Pathol. 2009; 22 (suppl. 1): 155A

Background: Minimal or "insignificant" prostatic adenocarcinoma (MinPCa) is defined as tumors with insufficient virulence to threaten survival. Given recent suggestion of TMPRSS2-ERG gene fusion association with aggressive PCa phenotype, we aimed to evaluate incidence of TMPRSS2-ERG fusion in MinPCa in comparison with grade matched "non-minimal" size PCa.
Design: All 33 prostatectomies classified as containing MinPCa (2002-2003) were retrieved. Diagnois of MinPCa (Gleason Score 6 PCa with total tumor volume < 0.5 CC, single section) was confirmed by a urologic pathologist. Tissue microarray (TMA) was constructed from the 33 cases where each tumor and paired benign tissue was represented by up to triplicate, 1mm, spots. TMA sections of 59 additional archival PCa were used as controls (26 pT2 non-minimal in size, 31 pT3a and 2 pT3b). FISH analysis was performed using break-apart probes for 5' and 3' regions of ERG. Each spot was scored for presence of TMPRSS2-ERG fusion through

deletion or translocation as well as for polyploidy (≥ 3 copies) at the ERG locus. At least 50 cells were scored per tumor.
Results: MinPCa: TMPRSS2-ERG fusion was identified in 46% (16/35) of MinPCa. In 87% (14/16) of positive tumors, fusion was due to deletion. The remaining 13% (2/16) of fusions were based on the demonstration of a split in the two juxtaposed probe signals. Ch21 polyploidy ± fusion and duplication of ERG deletion were not observed in any MinPCa case. Control group: TMPRSS2-ERG fusion was identified in 59% (35/59) of tumors. In 77% (27/35) of positive tumors, fusion was due to deletion. Ch21 polyploidy with ± fusion was present in 13/59 (22%) while polyploidy with duplicate ERG deletion was found in 6/59 (10%) of control tumors. On statistical analysis, there was no significant difference in TMPRSS2-ERG fusion incidence between the MinPCa and control groups ($p = 0.2$). Statistically significant higher rates of ch 21 polyploidy ± fusion was present in control group ($p = 0.0002$). A trend approaching statistical significance for higher incidence of ch21 polyploidy with duplicate deletion was also present in the control group ($p = 0.052$).
Conclusions: TMPRSS-ERG fusion rate of 46% is present in MinPCa. The latter is not significantly different from rate of fusion in control group of non-minimal pT2 and pT3 PCa. A higher rate of Ch21 polyploidy is detected in the control group compared to MinPCa. Our finding of a comparable rate of TMPRSS2-ERG fusion in MinPCa and non-minimal PCa argues against its value as a marker of aggressive PCa phenotype.

Editorial Comment

With higher number of prostate cancer detected in stage T1c due to screening, a higher number of small adenocarcinomas have been detected on needle biopsies. Many of these small adenocarcinomas may have criteria for minimal or "insignificant" cancer: tumor in no more than 2 cores, absence of Gleason grade 4 or 5, tumor not occupying more than 50% of the core, and favorable PSA density (1). It is important to note that these criteria relate to tumor volume and not biological behavior. It would be of utmost importance to know whether a minimal or "insignificant cancer" would behave as a latent (dormant or indolent) cancer or evolve to a clinical cancer.

A notable discovery related to the molecular aspect of prostate carcinoma was the identification by Tomlins et al. (2) of a recurrent chromosomal arrangement encountered in the majority of prostate carcinomas that they studied. Possible rearrangements are of two general types. In the first, the promoter and/or enhancer elements of one gene are aberrantly juxtaposed to a proto-oncogene, thus causing altered expression of an oncogenic protein. In the second, the rearrangement fuses two genes, resulting in the production of a fusion protein that may have a new or altered activity. Tomlins et al. (2) identified recurrent gene fusions of the region of TMPRSS2 to ERG or ETV1 in prostate cancer tissues. TMPRSS2 (21q22.2) is a prostate-specific gene that is present in normal and neoplastic prostate tissue and is strongly induced by androgen in androgen-sensitive prostate cell lines. ERG (21q22.3) and ETV1 (7p21.2) are genes that encode ETS family transcription factors. TMPRSS2:ERG fusion is more frequent and occurs due to a deletion of a region on chromosome 21. TMPRSS2: ETS fusion prostate cancers comprise 40-50% of the PSA screened hospital based prostate carcinoma examined to date, making it the most common genetic rearrangement in human cancer. Emerging data suggested that TMPRSS2:ERG prostate cancer is associated with higher tumor stage and prostate specific death. Therefore, this fusion may be a marker for aggressive prostate cancer.

The study by Albadine et al. found that TMPRSS-ERG fusion rate of 46% is present in minimal or "insignificant" prostate cancer. This finding is not significantly different from rate of fusion in control group of non-minimal confined cancer (pT2) or with extraprostatic extension cancer (pT3). The comparable rate of TMPRSS2-ERG fusion in minimal prostate cancer and non-minimal prostate cancer argues against its value as a marker of aggressive prostate cancer phenotype.

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Are nephrogenic adenomas renal stem/progenitor cell-derived lesions? An immunohistochemical study

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Background: Nephrogenic adenoma (NA) is a benign tumor-like lesion of the urinary tract that histologically resembles the developing distal nephron. Recent evidence suggests that NA is truly a "nephrogenic" lesion, arising from downstream seeding of shed renal tubular cells with implantation and proliferation in areas of damaged urothelium. This proposed pathogenesis and the rarity of the lesion suggest the possibility that NAs arise from kidney stem/progenitor cells that retain the ability to proliferate and develop into renal tubule-like structures when implanted at a distant site. Renal stem/progenitor cells have recently been identified in adult kidney tubules with several markers, including CD133 and PAX2. In our study, we investigate the expression of stem cell surface markers CD133 and CD44 as well as renal-specific transcription factors PAX2 and PAX8 by immunohistochemistry.
Design: Twenty-nine cases of NA from 2000 to 2004 were retrieved from the tissue archives, 18 of which were from urinary bladder and 19 from prostatic urethra. CD133, CD44, PAX2, and PAX8 immunohistochemical staining was performed using the avidin-biotin peroxidase method following antigen retrieval. Complete circumferential membranous staining was considered positive for CD133 and CD44. Distinct nuclear staining was required for PAX2 and PAX8 positivity.
Results: All NAs were positive for renal-specific transcription factors PAX2 and PAX8, consistent with previous studies. CD133 staining was detected focally in eight of 29 (28%) cases. The CD133 positive cells were seen in papillary surfaces, small tubules, and occasionally in the stroma. CD44 staining was detected in seven of ten cases, including five CD133 positive lesions. In the CD44 positive/CD133 positive cases, CD44 was present in the corresponding CD133 areas. CD44 expression, however, was also seen in other areas and in two CD133 negative cases. No staining for these for markers was identified in the epithelium or stroma in prostatic glands, prostatic urethra, or urinary bladder.
Conclusions: Stem cell markers CD44 (70%) and CD133 (28%) were identified in a subpopulation of cells in nephrogenic adenomas, all of which were also positive for renal-specific transcription factors PAX2 and PAX8. Therefore, we suggest that nephrogenic adenomas may arise from transplantation and proliferation of primitive renal cells into an extrarenal stem cell niche. The expression of additional stem cell markers in this regard is currently under investigation.

Editorial Comment

Nephrogenic adenomas usually arise in the setting of prior urothelial injury, such as past surgery, calculi, or trauma. An intriguing and elegant study was able to demonstrate a derivation from renal tubular cells occurring in renal transplant patients.

Mazal et al. (1) reported that the sex-chromosome pattern in examples of bladder nephrogenic metaplastic lesions in the recipient reflected the pattern of the donor patient, and was different from the chromosome pattern of adjacent urothelium in the recipient patient. An additional support for nephrogenic adenomas arising from shed renal tubular cells is positivity for PAX2. Tong et al. (2) reported that 100% of a series of 39 examples of nephrogenic adenomas stained with PAX2, a renal transcription factor which is specific for tubular epithelium. Urothelium and prostate epithelium do not stain with this antibody. These studies support that nephrogenic adenoma is not of urothelial origin and most probably originates from implanted cells shed from renal tubules.

Devaraj et al. considered the possibility that nephrogenic adenomas arise from kidney stem/progenitor cells that retain the ability to proliferate and develop into renal tubule-like structures when implanted at a distant site. They investigated the expression of stem cell surface markers CD133 and CD44 as well as renal-specific transcription factors PAX2 and PAX8 by immunohistochemistry. Renal stem/progenitor cells have recently been identified in adult kidney tubules with several markers, including CD133 and PAX2. Stem cell markers CD44 (70%) and CD133 (28%) were identified in a subpopulation of cells in nephrogenic adenomas, all of which were also positive for renal-specific transcription factors PAX2 and PAX8. These findings suggest that nephrogenic adenomas may arise from transplantation and proliferation of primitive renal cells into an extrarenal stem cell niche.

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BASIC AND TRANSLATIONAL UROLOGY

Oestrogen receptor expression and neuronal nitric oxide synthase in the clitoris and preputial gland structures of mice

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Objective: To study the presence of oestrogen receptors (ER) and neuronal nitric oxide synthase (nNOS) in the mouse clitoris.
Materials and Methods: A series of sections of the pelvic area, including the preputial glands and clitoris, of 10 mice were assessed by immunocytochemical studies specific for ER-alpha and -beta, and nNOS; selected sections were also stained with Masson's trichrome.
Results: ER alpha was detected in the epithelium of the gland of the clitoris, and in the glandular tissue, preputial and apocrine gland. ER alpha was detected in the nuclei of stromal cells around the cavernous tissue and near the epithelium of the clitoris. Cytoplasm ER alpha was detected in a few cells in an area ventral to the clitoral

gland. There was also nuclear staining in the connective tissue cells surrounding the clitoris. Very light ER beta immunostaining was detected in the clitoris and in the tissue related to it. There were some cells with nuclear staining in the vessels of the cavernous tissue of the clitoris. nNOS immunostaining was detected in the clitoris, the preputial gland and the connective tissue.
Conclusion: ER alpha and beta isoforms, and nNOS, are present in the clitoris and preputial glands of female mice in different cellular locations and with differing levels of receptivity. Functional studies would further elucidate the role of receptor functions and their relationship to the neuronal expression of NO.

Editorial Comment

The authors are to be commended for this interesting study, which provided additional knowledge on the presence of estrogen receptors alpha (ERα) and beta (β), as well as on neuronal nitric oxide synthase (nNOS) and their relationships, in the mouse clitoris.

It was found a diffuse and deep immunostaining for ERα in the epithelium of the gland of the clitoris, and in the glandular tissue and prepuce. Also, ERα was detected in the nuclei of stromal cells around the cavernous tissue and near the epithelium of the clitoris. On the other hand, the authors found very few ERβ immunostaining in the clitoris and in the tissue related to it. However, there were some cells with nuclear staining in the vessels of the cavernous tissue of the clitoris.
In a similar pattern of ERα, although not too strong, nNOS immunostaining was detected in the clitoris, the preputial gland and connective tissue.

Concerning the epithelium of the vaginal wall, it was negative for the immunostaining for ERα and β. Membrane-based nNOS was found in the vaginal wall, and not along the upper vaginal wall, but only in one part, closest to the vaginal opening.

The authors proposed that the nuclear immunostaining for ERα in the stroma of the clitoris suggests a higher receptivity to this hormone. All receptors identified in the clitoris tended to be more intensely expressed in stromal than epithelial cells, suggesting that there is a stromal - epithelial interaction induced by the different sex steroids. ERβ immunostaining was only detected in a few cells in the vascular lumen of the cavernous tissue of the clitoris.

By contrast, with ERα, the study showed that there was no staining in the glandular tissue, epithelium or stroma of the clitoris. The authors speculate that these results suggest that ERβ is not essential for the normal functions that take place in the clitoris of the mouse.

nNOS was immunodetected with a similar pattern of distribution to that of ERα. Therefore, the authors proposed that NO might play a role in controlling blood flow and capillary permeability, the mechanisms of sexual lubrication due to cGMP action, induced by NO. The homeostasis of this system needs cGMP breakdown. It is possible that the physiological response to sexual arousal in the female follows the same biochemical pathway as in the male.

The new knowledge presented in this work, concerning the relationship of estrogen receptivity in the genital sensory field and clitoral vasculogenic processes, represent and important advance in the understanding of the presence and anatomical location of nNOS and ER isoforms.

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Natural orifice translumenal endoscopic surgery (NOTES) renal cryoablation in a porcine model

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Objective: To present our laboratory experience with natural orifice translumenal endoscopic surgery (NOTES) renal cryoablation.
Materials and Methods: In two female farm pigs, we performed four procedures of NOTES renal cryoablation. In each pig, NOTES was performed through a transgastric approach and a transvaginal approach for each kidney, respectively. The pig was placed in the flank position and pneumoperitoneum obtained using a transabdominal Veress needle. In the first pig, we started with the left kidney with a transgastric approach: a dual-channel video gastroscope (Olympus, Tokyo, Japan) was used, the stomach wall was punctured using a needle-knife, a guidewire was passed into the abdominal cavity and the access dilated using a controlled radial expansion balloon. The bowel was mobilized medially and the Gerota's fascia overlying the upper pole was dissected. Under direct endoscopic vision, a cryoablation probe was introduced percutaneously into the anterior upper pole of the kidney. The pig was then flipped to the right flank position and a transvaginal approach was used: the gastroscope was introduced through the posterior fornix of the vagina. For the second pig, we performed initially a transgastric right-side cryoablation then a transvaginal left-side cryoablation as described for the first pig.
Results: All four procedures were performed successfully, with no intraoperative complications. No additional laparoscopic ports or open conversions were necessary. The vision of the kidney and the ice-ball was adequate for all cases. The mean operative duration was 83 min. Stomach closure was tested watertight, and there were no abdominal or pelvic injuries found at autopsy.
Conclusions: NOTES can provide adequate minimal surgical dissection for safe and effective percutaneous renal cryoablation under direct videoscopic monitoring at kidney locations otherwise not accessible percutaneously. Both transgastric and transvaginal approaches can be used effectively for renal cryoablation providing a minimally invasive scar-less surgery.

Editorial Comment

This is an interesting bench to bedside research, demonstrating the usefulness of the pig model for research in endourology and videoendoscopy. It has been shown that the pig is the best animal model for translational research in urology, due to its renal similarities with humans, concerning intra-renal anatomy of collecting system, arteries and veins (1-3). Also, abdominal and pelvic cavities in pigs are similar to humans, both in volume and in organ position. So, it is possible to transpose the laboratory research to clinical setting very fast.

The present paper clearly demonstrated the feasibility of NOTES for videoendoscopic monitoring of percutaneous renal cryoablation both by transgastric and transvaginal approaches.

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UROLOGICAL ONCOLOGY

Prevalence and risk factors of bisphosphonate-associated osteonecrosis of the jaw in prostate cancer patients with advanced disease treated with zoledronate

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Background: In addition to other treatments, patients with prostate cancer (pCA) and bone metastasis receive bisphosphonates. Since 2003, a previously unknown side-effect of bisphosphonates-bisphosphonate-associated osteonecrosis of the jaws (BP-ONJ)-has been described, and frequency has since increased. An exact incidence is still unknown.
Objectives: The aim of this study was to assess the incidence and additional factors in the development of BP-ONJ.
Design, Setting, and Participants: From July 2006 to October 2007, patients with advanced pCA and osseous metastasis receiving bisphosphonate therapy in the Department of Urology or Haematology and Oncology at the Johannes-Gutenberg-University Mainz, Germany, received a dental examination. In all, 43 patients were included.
Measurements: Patients were checked for exposed bone, osteonecrosis, mucosal defects, inflammation, and oral hygiene. Further points were the applied bisphosphonate, co-medication, the duration of application, and possible trigger factors for BP-ONJ.
Results and Limitations: Eight of 43 patients developed BP-ONJ (18.6%). All patients had received zoledronate at least 14 times. Two patients had received bondronate, and one patient had received pamidronate before switching to zoledronate. All patients had had a previous tooth extraction or a denture pressure sore, and all patients had received additional chemotherapy and corticosteroids.
Conclusions: The reason for this relatively high incidence compared to other studies might be the prospective study design and thorough dental examination. In studies with such small numbers as have been published to date, nondetection or nonreported cases of BP-ONJ have an influence on the outcome. The incidence of BP-ONJ in patients with pCA might be an underestimated problem.

Editorial Comment

Bisphosphonates are widely given in patients with a high risk for, or manifest, bone metastases. In most patients with advanced prostate cancer, this drug is considered standard therapy. Recently, the risk for developing dental complications became evident but neither the true incidence nor risk factors are known. This paper helps to clarify the situation.

Nearly 19% of patients from this uncontrolled series suffered from some sort of osteonecrosis. Most were highly pretreated with biphosphonates and steroid and/or docetaxel therapy. Urologists should be aware

of this possible complication and should work closely together with experienced dentists. Special attention should be given to multimodally treated patients.

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Long-term survival after gemcitabine and cisplatin in patients with locally advanced transitional cell carcinoma of the bladder: focus on supplementary treatment strategies
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Objective: The objective was to evaluate response and survival, as well as efficacy of subsequent supplementary treatment and follow-up strategy in patients with locally advanced transitional cell carcinoma of the bladder following combination chemotherapy with gemcitabine and cisplatin (GC).
Methods: A total of 84 patients with locally advanced (T4b, Nx, M0 or Tx, N2-3, M0) received GC. After chemotherapy, the strategy was close surveillance in patients with complete response, and supplementary radical cystectomy or radiotherapy whenever possible in patients with partial response.
Results: A total of 25 patients (29.8%) with complete response to chemotherapy were followed by close surveillance. This group achieved a median overall survival of 47.6 mo. Another 25 patients had partial response to chemotherapy. Of these patients, 16 had supplementary treatment, with 10 achieving "no evidence of disease" (NED). Thus, a total of 35 patients achieved NED with a median overall survival of 48.7 mo versus 10.2 mo in patients not achieving NED (hazard ratio=0.10; 95%CI, 0.05-0.20; $p<0.0001$). The rate of NED was higher in the group of patients who had a cystectomy compared with the group who received radiotherapy as supplementary treatment.
Conclusions: In patients with locally advanced bladder cancer, NED following chemotherapy alone or chemotherapy plus supplementary cystectomy or radiotherapy is essential to achieve long-term survival. Patients with a partial response should be offered radical cystectomy whenever possible, which seems to be superior to radiotherapy. Close surveillance may be an alternative to immediate cystectomy in patients with complete response following chemotherapy.

Editorial Comment

Patients with locally advanced bladder cancer cannot be cured by surgery or radiotherapy alone. Systemic cytotoxic chemotherapy is the only option here. In contrast to patients with visceral metastases, patients without distant metastases and locoregional disease form a group with rather favorable prognosis. A group of 84 patients with this disease was analyzed for long-term survival after Gemcitabine-Cisplatinum (GC) – based chemotherapy.

Median overall survival of the group was 16.3 months. There was a significant difference between patients who had no evidence of disease (NED) after GC or after GC and supplementary treatment (e.g. cystectomy) in comparison to those who had a partial response and underwent supplementary treatment. Median survival in the first and second groups was nearly 48 months whereas the third group had less than 12 months median survival. Patients who underwent cystectomy as treatment after GC significantly fared better than patients who received

radiotherapy. In conclusion, relative long-term survival is possible in this cohort of patients and multimodal treatment should aim at eradicating all disease possible.

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NEUROUROLOGY & FEMALE UROLOGY

Nonsurgical transurethral collagen denaturation for stress urinary incontinence in women: 12-month results from a prospective long-term study

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Study Objective: To assess efficacy of nonsurgical transurethral collagen denaturation (Renessa) in women with stress urinary incontinence (SUI) caused by bladder outlet hypermobility.
Design: Continuing, prospective, 36-month, open-label, single-arm clinical trial. Twelve-month results from intent-to-treat (ITT) analysis are reported. Canadian Task Force classification II-2.
Setting: Thirteen physician offices or ambulatory treatment centers.
Patients: Women with SUI secondary to bladder outlet hypermobility for 12 months or longer who failed earlier conservative treatment and had not received earlier surgical or bulking agent therapy.
Interventions: Women were treated as outpatients and received an oral antibiotic and local periurethral anesthesia before undergoing treatment with transurethral radiofrequency collagen denaturation.
Measurements and Main results: Voiding diaries and in-office stress pad weight tests yield objective assessments. Subjective measures include the Incontinence Quality of Life (I-QOL), Urogenital Distress Inventory (UDI-6), and Patient Global Impression of Improvement (PGI-I) instruments. In total, 136 women received treatment (ITT population). Patients experienced significant reductions versus baseline in median number of leaks caused by activity/day and activity/week ($p < .0026$ for both), with 50% of patients reporting 50% or more reduction. Pad weight tests revealed that 69% of women had 50% or more reduction in leakage (median reduction 15.2 g; $p < .0001$); 45% were dry (29% no leaks; 16% < 1-g leakage). Significant improvements occurred in median scores on the I-QOL (+9.5 [range -66.0 to 91.0]; $p < .0001$) and mean scores on the UDI-6 (-14.1 +/- 24.7; $p < .0001$). Furthermore, 71.2% showed I-QOL score improvement, including 50.3% with 10-point or greater improvement, and 49.6% reported on the PGI-I that they were “a little,” “much,” or “very much” better. Conclusion: At 12 months, treatment of SUI with nonsurgical transurethral collagen denaturation resulted in significant improvements in activity-related leaks and quality of life.

Editorial Comment

Authors report on the therapy of female stress urinary incontinence using transurethral radiofrequency (RF) collagen denaturation. This report entails the 12-month results from an ongoing 36-month intent to treat study. The authors identified the following: no significant adverse events; that the procedure was very well tolerated; and using this minimally invasive technique, results similar to transurethral bulking agents were obtained.

This review revisits a new technology which has been previously surveyed in this journal (1). In that study, the authors noted the safety of the therapy as well as its clinical efficacy when reported in comparison to a sham treatment. Though the study did report a significant number of patients who were lost to follow-up, withdrew consent, or opted for surgery, this is not unexpected in view of the large number of study centers (13 centers) which were incorporated into the study. Of note is that the procedure appears to be very safe, very fast and highly competitive with bulking therapy in the patient with urethral hypermobility. This refined application of the radiofrequency energy to alter collagen is distinctly different from the ablative therapy used for neoplastic conditions or benign gynecological diagnoses. Though the therapy does not appear to preclude further surgery, it should be avoided in patients who already have injectable therapy secondary to potentially variable application of the energy to the periurethral implant. That this technology may be applied in the office with the use of a local periurethral anesthetic and has a very short post-procedure convalescence period renders it a therapeutic option that warrants a close review by treating physicians.

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Urethral diverticula in 90 female patients: a study with emphasis on neoplastic alterations

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Purpose: Urethral diverticula are uncommon and occur predominantly in women. We examined a large series of female urethral diverticula to determine associated neoplastic alterations and subsequent clinical outcomes.
Materials and Methods: All pathological evaluations of female urethral diverticulectomies performed at our institution between 1981 and 2007 were retrospectively reviewed and the clinicopathological features were correlated.
Results: During this period 90 women underwent urethral diverticulectomy at our institution. Patient age was 24 to 78 years (mean 45). The most common clinical finding was urinary incontinence (29 of 78 women or 37%). Diverticular size was 0.3 to 5.0 cm (mean 1.7). Neoplastic alterations identified in 5 patients (6%) were glandular in nature, including 1 clear cell and 4 invasive adenocarcinomas. Superficial changes associated with invasive carcinoma included villous adenoma in 1 case, intestinal metaplasia in 2 and high grade dysplasia in 3. An additional 3 patients had extensive intestinal metaplasia. Of the 90 patients the remaining 82 demonstrated benign findings, including nephrogenic adenoma in 10 (11%). All 5 patients with invasive carcinoma underwent anterior pelvic exenteration with urinary diversion. In 2 patients with invasive adenocarcinoma metastatic disease subsequently developed, of which they died.
Conclusions: Although most cases of surgically resected diverticula demonstrate benign features, approximately 10% show atypical glandular findings, including invasive adenocarcinoma. Due to the risk of malignancy in a

subset of patients careful clinical examination and followup are warranted in all patients to exclude neoplastic disease.

Editorial Comment

The authors report on an impressive numerical series of 90 patients who underwent urethral diverticulectomy. The most common associated clinical finding with the urethral diverticulum was urinary incontinence. Pathologic evaluation of the resected tissue revealed 10% with atypical glandular findings; consequently, the authors urged the readership to have careful follow-up in those patients secondary to the association with invasive adenocarcinoma.

This large series on urethral diverticula warrants reading and review by those actively involved in female urology. Though the most common clinical finding associated with urethral diverticulum was urinary incontinence, 4 out of the 5 patients who had a carcinoma of the involved urethral diverticulum presented with urinary retention. In addition, the authors noted that a review of the position of nephrogenic adenomas throughout the urothelial tract identified a higher prevalence in the urethral diverticulum. This would be something to keep in mind on evaluating a urethral diverticulum that is associated with a submucosal mass. The high mortality rate quoted in this series for patients with invasive adenocarcinoma involving a urethral diverticulum highlights the importance of close follow-up in those patients that have atypical glandular findings on pathologic analysis of the resected diverticulum.

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PEDIATRIC UROLOGY

Updated experience with the Monti catheterizable channel

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Objectives: The Monti catheterizable channel is used as an integral part of continent bladder reconstruction in children. We have updated our ongoing experience at Riley Children's Hospital with 199 patients.
Methods: We identified 199 patients for retrospective review, including all patients for whom a Monti ileovesicostomy was created from January 1997 to August 2004. We assessed the complications, surgical procedures, and stomal continence.
Results: At mean follow-up of 28 months, we found that 194 of 199 patients (97.5%) continued to use their Monti catheterizable channel for bladder drainage. Early surgical complications occurred in 7 patients (3.5%), usually in those who had undergone simultaneous bladder augmentation (5 of 7). Revision was required in 16 patients (8%) for stomal stenosis (n = 11), prolapse (n = 2), or superficial stomal problems (n = 3). Of the 199 patients, 17 (8.5%) required 19 bladder or channel revisions. The primary indications were related to elongation and angulation of the channel in 7 and deficient tunnel length in 8. Minor difficulty with catheterization was noted in 16 patients (8%), and endoscopy with minor procedures was required in 4 patients (2%). Leakage from the channel was uncommon, occurring in only 4 of 115 patients (3.5%).

Conclusions: With increasing demand for simultaneous appendicocecostomy for stool continence at bladder reconstruction, we continue to use the Monti ileovesicostomy for bladder drainage. Our experience with nearly 200 patients has demonstrated the durability and success of this technique.

Editorial Comment

During a seven-year period, 199 patients underwent a Monti catheterizable stoma procedure, 90 male and 109 females. Eighty-eight percent of the patients had a neuropathic bladder and over 97% of the patients underwent an additional simultaneous procedure. Seventy percent of them had bladder augmentations at the same time. Seven patients (3.5%) had early surgical complications. Sixteen (8.0%) had stomal revisions and 19 patients (9.5%) underwent channel revisions. Sixteen (8.0%) of the patients had difficulty catheterizing and 4 (3.5%) had incontinence after the channel was made.

The authors conclude that this is a favorable outcome to a catheterizable stoma. This is their procedure of choice when the appendix is used for appendicocecostomy bowel irrigation regimen. They preferred a spiral Monti technique whenever a longer channel is required, rather than a double Monti technique.

The authors have a mean follow up of 28 months and their results are favorable compared to their own and another study in the literature. Even though the complication rate seems high, these patients benefit greatly from a continent catheterizable stoma. Most of the complications and revisions are on the stoma and channel itself and the channel can be made functional and the patients and caregivers will be highly satisfied.

It should be noted that one or two other complications were in non-compliant patients and particularly when a continent catheterizable stoma is considered, careful attention to patient compliance before the surgery is performed will minimize these unfortunate complications afterwards. If the catheterizable stoma is not used for a brief period of time, often it closes and cannot be recovered.

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Corporeal grafting for severe hypospadias: a single institution experience with 3 techniques

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Purpose: Correction of severe chordee by corporeal body grafting has been successfully performed using various grafts and biomaterials. We report a single institution comparison of our experience using small intestinal submucosa, tunica vaginalis and dermal grafts at stage 1 hypospadias repair.
Materials and Methods: A retrospective chart review was performed of the records of all patients who underwent staged hypospadias repair from 1985 to 2006 with corporeal body grafting at stage 1 with small intestinal submucosa, tunica vaginalis or dermal grafts. Age at grafting, time between stages, residual chordee at stage 2 repair and the need for additional plication or chordee correction at stage 2 were recorded.
Results: A total of 71 patients were identified with a median age of 10 months at stage 1 repair and a median of 7.6 months between stages 1 and 2 repair. Dermal grafts, tunica vaginalis and small intestinal submucosa grafts were used in 29, 21 and 20 patients, respectively. One patient received a combination of small intestinal submucosa and tunica vaginalis. None of the patients receiving tunica vaginalis graft required any further correction of chordee. One patient with a dermal graft and 1 receiving small intestinal submucosa required Nesbit

plication at stage 2 repair for minor ventral chordee. One patients receiving small intestinal submucosa showed severe fibrosis at the graft site, requiring excision and repeat grafting with tunica vaginalis. This patient has been previously described. The 2 patients with small intestinal submucosa related complications had 4-ply grafts. We have seen no complications associated with 1-ply small intestinal submucosa. At limited followup we have not seen residual chordee after stage 2 repair.
Conclusions: In a large group of children requiring corporeal grafting for severe chordee we observed successful chordee correction with 1-ply small intestinal submucosa, tunica vaginalis or dermal grafts.

Editorial Comment

A 20-year experience of corporeal grafting in a staged hypospadias procedure is reported. Grafts were either small intestine submucosa, tunica vaginalis or dermal grafts. All of the patients have completed a second stage hypospadias repair. The urethral plate was divided when routine maneuvers to correct chordee still left 45° of ventral curvature. Tunica vaginalis was used as a graft in all the cases rather than a flap and each of the grafts were approximately 25% larger than the corporeal defect that was created to correct the chordee. Graft placement and success were verified after suturing the graft in place by an artificial erection.

Initially for the SIS graft, 4-ply SIS was used in 12 patients and subsequently 1-ply has been used. Of the 71 patients in this study, the median age was 10 months. 29 dermal grafts, 21 tunica vaginalis grafts and 20 SIS grafts were used. One of the dermal graft patients and one of the 4-ply SIS patients required a subsequent repair. The authors concluded that each of the grafting materials were successful. They note that they have not used 4-ply SIS for several years and that long-term and post-pubertal outcome is not available.

This manuscript shows that over two decades, several types of grafting materials have been used and each showing good success. In skilled hands, there is not a reason to choose one graft material over another. The second stage of the repair was not made more difficult by any of the graft procedures and it is heartening to know that the surgeon can make a personal and patient-appropriate choice and expect good outcomes.

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