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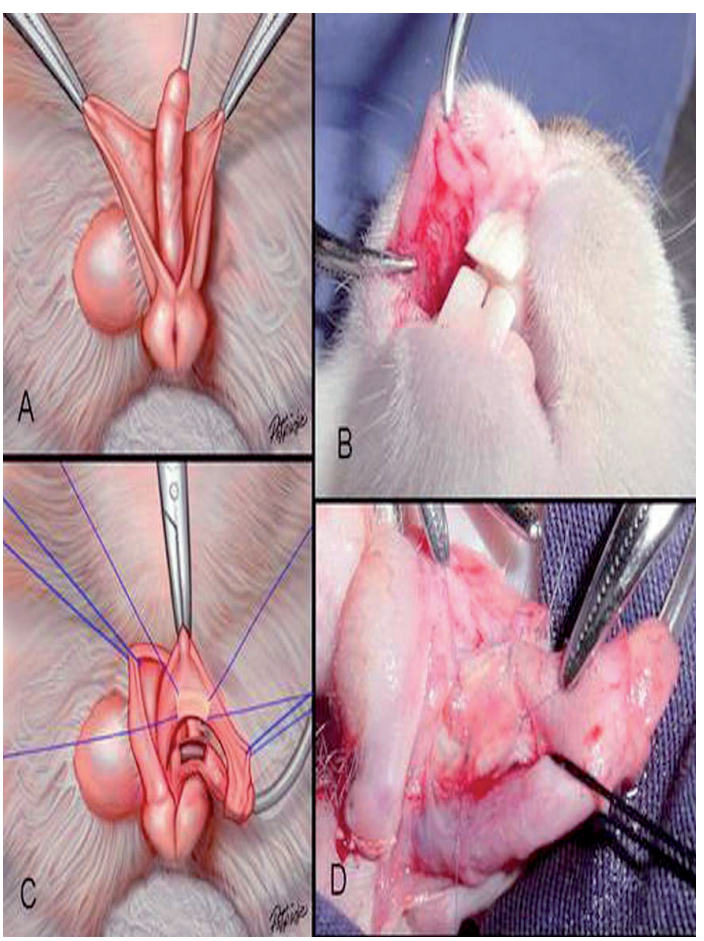

Urethroplasty with Dorsal Buccal Mucosa: Experimental Study (Page 345)

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EDITOR'S COMMENT

LH-RH Analogue for Unilateral Cryptorchidism

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

Doctor Hadziselimovic, from Kindertagesklinik, Liestal, Switzerland, confirmed on page 319 that LH-RH analogue (LH-RHa) treatment induces an increase in maturation of the germ cells. The author studied 30 unilateral cryptorchid boys, with an average age of 3 years at the time of surgery. Testicular biopsy showed that they had impaired testicular maturation and were therefore at high risk for infertility. Fifteen of the 30 unilateral cryptorchid boys were treated with 10 μg LH-RHa (Buserelin) nasal spray, administered on alternate days for a period of 6 months, following orchiopexy. The control group consisted of 15 cryptorchid boys who had been treated by Schoemakers type of orchiopexy, alone. After puberty, the ejaculates of both groups were analyzed. He found that all males in the untreated group were severely oligospermic, with 20% being azoospermic. In contrast, 86% of the treated ex-cryptorchid males had a sperm concentration within the normal range. For the first time it was demonstrated that infertility in cryptorchidism could be successfully corrected when suitably treated with a LH-RHa. This innovative hormonal treatment will have a profound effect on the current recommended surgical treatment of boys with undescended testes. Dr. Marcelo Braz, form Bonsucesso Hospital, Rio de Janeiro, Brazil, and Dr. Luciano Favorito, form the Urogenital Research Unit, Rio de Janeiro, Brazil, provided editorial comments on this article.

Doctor Souza and co-workers, from Federal University of Sao Paulo, Brazil, developed on page 345 an experimental model to assess the histological characteristics of dorsal buccal mucosa graft urethroplasty when used dorsally to reconstruct the urethral plate. They used 12 New Zealand rabbits with a surgically created dorsal penile urethral defect. A buccal mucosa graft was sutured to the corpora and tunica albuginea, and the ventral urethra anastomosed to this new urethral plate. The animals were divided in groups 1, 2 and 3 and sacrificed 1, 3 and 6 weeks after surgery. In group 1 the histopathological analysis showed submucosal lymph-mononuclear inflammatory edema, numerous eosinophils and squamous epithelium integrated into the adjacent urothelium. In group 2 there was no evidence of an inflammatory response but rather complete subepithelial hyaline healing, which was more marked in group 3. The authors concluded that the healing of buccal mucosa grafts to reconstruct the urethral plate can be achieved by total integration of the squamous epithelium with the urothelium, maintaining the original histological properties of the graft with no fibrosis or retraction. Dr. Massimo Lazzeri and Dr. Guido Barbagli, from the Center for Reconstructive Urethral Surgery, Arezzo, Italy, Dr. Raimund Stein, from the University of Mainz, Germany, and Dr. Alchiede Simonato and Dr. Andrea Gregori, from the University of Genoa, Italy, provided excellent editorial comments on this paper.

Doctor Frota and colleagues, form the Glickman Urological Institute, Cleveland Clinic Foundation, Ohio, USA, reviewed on page 259 the current status of laparoscopic radical prostatectomy (LRP) and robotic assisted radical prostatectomy (RALP) in relation to radical retropubic prostatectomy (RRP) in the manage-

ment of localized prostate cancer. The authors concluded that after intermediate term follow-up, LRP and RALP achieved similar oncologic and functional results compared to RRP. However, LRP and RALP were associated with decreased blood loss, faster convalescence and better cosmetics when compared to RRP. The RALP technique is undoubtedly more expensive. Dr. Julio Pow-Sang, from the University of South Florida College of Medicine, Tampa, Florida, USA and Dr. Lambda Msezane and Dr. Scott Eggener, from the University of Chicago, Illinois, USA, provided important editorial comments on this manuscript.

Doctor Eandi and associates, form the University of California Davis, Sacramento, California, USA, evaluated on page 336 their experience with tension-free transvaginal tape (TVT) placement for the management of stress urinary incontinence (SUI) in women who had previously undergone a failed midurethral synthetic sling (MUS) procedure. After studying 10 patients available for follow-up at a mean period of 16 months, they found that 4 of the 10 patients achieved complete continence, and another 3 patients reported significantly improved continence and quality of life. Three women stated that their continence did not improve. They concluded that TVT placement may be a viable option for the management of women with persistent or recurrent SUI following an initial MUS procedure. Dr. Mayank Mohan Agarwal and Dr. Ravimohan Mavuduru, from Postgraduate Institute of Medical Education and Research, Chandigarh, India and Dr. Alexander Tsivian, from Tel Aviv University, Israel, provided editorial comments on this paper.

Doctor Asbagh and collaborators, from Celal Bayar University, Manisa, Turkey, investigated on page 354 the inhibitory effects of zoledronic acid (ZA) on tumor related growth factor IL-6 in hormone resistant prostate cancer cell lines. The association between apoptosis and IL-6 inhibition was also assessed. They found that PC-3 and DU145 cell lines were sensitive to ZA mediated cytotoxicity in a dose- and time-dependent manner. However, the apoptotic effect was significantly different among PC-3 and DU145 cells ($p < 0.05$). IL-6 secretion was significantly lower in both cell lines, compared to the untreated control cells ($p < 0.05$). Although the increased inhibition of IL-6 secretion was associated with increased apoptosis in DU145 cells ($p = 0.002$), there was no similar association for PC-3 cell line ($p = 0.347$). When compared to the untreated controls, the number of cDNA copies was significantly lower in the ZA treated DU145 cell line at doses of 30 and 90μM ($p < 0.05$), suggesting a reduced expression of IL-6 mRNA. The authors concluded that ZA exhibited a time- and dose-dependent apoptotic effect on PC-3 and DU145 prostate cancer cell lines and this effect was associated with inhibited secretion of IL-6 in DU145 cell line. Dr. Zoran Culig, from the Innsbruck Medical University, Austria, provided editorial comment on this paper.

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

Review Article

International Braz J Urol Vol. 34 (3): 259-269, May - June, 2008

Comparison of Radical Prostatectomy Techniques: Open, Laparoscopic and Robotic Assisted

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ABSTRACT

Introduction: To review the current status of laparoscopic radical prostatectomy (LRP) and robotic assisted radical prostatectomy (RALP) in relation to radical retropubic prostatectomy (RRP) in the management of localized prostate cancer.
Materials and Methods: Between 1982 and 2007 published literature was reviewed using the National Library of Medicine database and the following key words: retropubic, laparoscopic, robotic, robot-assisted, and radical prostatectomy. Special emphasis was given to the technical and cost considerations as well as operative, functional and oncologic outcomes. In particular, reports with pioneering work that have contributed to the evolution of the technique, presenting comparative outcomes and with large series encompassing intermediate/long term follow-up, were taken into account.
Results: After intermediate term follow-up, LRP and RALP achieved similar oncologic and functional results compared to RRP. However, LRP and RALP were associated with decreased blood loss, faster convalescence and better cosmetics when compared to RRP. The RALP technique is undoubtedly more expensive.
Conclusions: The oncologic and functional outcomes for LRP and RALP are similar to RRP after intermediate term follow-up. Long term follow-up and adequately designed studies will determine the inherent advantages and disadvantages of the individual techniques in the management of localized prostate cancer.

Key words: *prostate cancer; prostatectomy; laparoscopy; robotics*
Int Braz J Urol. 2008; 34: 259-69

INTRODUCTION

Prostate cancer accounts for approximately one third of cancer in men in the United States. Eighty-six percent of prostate cancer diagnosed in 2004 was localized with 5-year survival rates approaching 100% (1). Based on excellent survival rates, radical prostatectomy is considered the standard treatment for the management of localized prostate cancer (2).

Retropubic Radical Prostatectomy (RRP) was first reported by Millin in 1947 (3). However, the procedure was associated with significant blood loss, incontinence, impotence and prolonged convalescence. In the early 1980s, Walsh laid the foundations of anatomic RRP with better understanding of the prostate anatomy, specifically the dorsal vein complex and neurovascular bundle (NVB) (4). These results were associated with better functional outcomes without compromising oncologic principles.

The variability of RRP outcomes, introduction of laparoscopy in the urological armamentarium and the success of less invasive treatment alternatives (i.e. brachytherapy) in prostate cancer, have acceler-

ated the development of laparoscopic pelvic surgery (5). Schuessler et al. performed the first laparoscopic radical prostatectomy (LRP) in 1991 (6). Of note, the LRP technique has been refined and standardized by Guillonneau and Vallancien in the late 1990s and the procedure has gained popularity since then (7). In addition to the conventional advantages of minimal invasive surgery and reduced blood loss, the LRP technique, in expert hands, is safe and effective, and provides oncologic outcomes comparable to that of open RRP (7,8). However, LRP is a complex procedure associated with a steep learning curve and limited ergonomics.

Robotic assisted laparoscopic prostatectomy (RALP) was first reported by Abbou et al. in 2000 (9). RALP has been popularized by Menon et al. with an intention to decrease the steep learning curve of LRP while accomplishing the advantage of a minimally invasive technique (10). Advantages of the RALP technique include the 3-dimensional stereoscopic visualization, intuitive finger-controlled movements and the Endowrist technology (Intuitive Surgical, Sunnyvale, CA, USA) (11). Furthermore, improved ergonomic surgery can be achieved by a comfortably seated surgeon.

The RRP is the reference standard for the surgical management of localized prostate cancer. With wider availability of the minimally invasive radical prostatectomy techniques, there is a debate regarding what the standard treatment will be for the management of localized prostate cancer in the near future. It is also open to discussion as to whether experienced open surgeons should learn minimally invasive techniques. There are no prospective randomized studies, to our knowledge, comparing the three techniques (RRP vs. LRP vs. RALP) to date. In comparing the three techniques, several issues such as perioperative, functional and oncologic outcomes need to be addressed. Unquestionably, achieving optimum cancer control is the most important determinant followed by favorable functional outcomes. Another factor that influences treatment acceptance is the cost.

It is clearly important to address these issues in the urological literature. Therefore, in this review, we present the evolution and the recent data on the outcomes of RRP, LRP and RALP in the contemporary urological literature with a special emphasis on the technique, cost, operative, functional and oncologic outcomes.

SURGICAL TECHNIQUE

The standard surgical technique for RRP was described by Walsh (4). Other urologists have used additional anatomic and technologic advances to minimize morbidity associated with the procedure. Slabaugh and Marshall reported modified incisional techniques and noted that the mini-laparatomy RRP technique was associated with less operating room (OR) time and reduced cost compared to LRP (12). Mini-laparotomy was performed using an 8 cm low midline incision, wherein a laparoscopic camera lens was used for visualization. Sved et al. reported a RRP technique with a modified Pfannenstiel incision associated with better cosmetic results, less postoperative pain and lower analgesic requirement (13).

Four different LRP techniques including the transperitoneal antegrade technique, transperitoneal retrograde technique, extraperitoneal antegrade technique and extraperitoneal retrograde technique have been described (14). The antegrade transperitoneal approach is preferred at the Cleveland Clinic. Using the transperitoneal or the extraperitoneal approach, the senior author has performed more than 750 LRPs at our institution since 1999.

Our transperitoneal LRP technique has been previously reported (15). Briefly, the patient is placed in a modified lithotomy position with the arms adducted by the patient's side. The table is set in a 15-30 degree Trendelenburg position. Initially, five ports are placed in a fan-array (Figure-1). Bowel loops are gently retracted out of the pelvic cavity. An inverted U-shaped peritoneotomy incision along the undersurface of the anterior abdominal wall is made. Subsequently, the endopelvic fascia is freed from the fatty tissue bilaterally and incised using a J-hook eletrocautery or cold endoshears. The Foley catheter is replaced by a metallic urethral dilator to enhance needle orientation during dorsal vein ligation. The dorsal vein complex ligature is created with a 2-0 Vicryl (CT-1 needle) stitch. The posterior bladder neck is deeply scored with a J-hook eletrocautery at the proposed line of transection at a safe distance

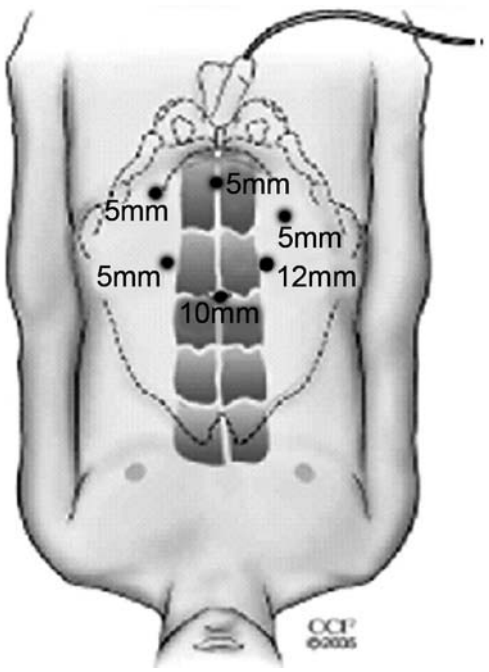

***Figure 1** – Port placement during laparoscopic radical prostatectomy.*

from the ureteric orifices. The vas deferens is clipped with a Hem-o-lock clip and divided. The NVB is released in an antegrade manner along the convexity of the prostate, using a combination of sharp scissor cuts and gentle blunt teasing with a soft laparoscopic Kittner. The dorsal vein complex is divided, followed by apical dissection and urethral transection. Urethrovesical anastomosis is accomplished with a watertight double-needle running suture technique using 2-0 Monocryl in two different colors. A 20 Fr Foley catheter is inserted into the bladder. A Jackson-Pratt drain is placed in the pelvis, the specimen is removed by extending the umbilical port site incision and port sites are closed.

The extraperitoneal approach provides a rapid access to the space of Retzius, minimizes bowel complications and intra-abdominal organ damage. However, recent studies comparing transperitoneal versus extraperitoneal approaches have not found any significant differences (16,17). The extraperitoneal approach may be preferable in obese patients as it may shorten the distance between the trocar insertion site and operative field, and in patients with previous abdominal surgery where time-consuming adhesiolysis is avoided and the risk of bowel injury is minimized (14).

LRP renewed interest in the periprostatic neuroanatomy because of the superior image quality and enhanced magnification. Technical modifications during LRP have mainly focused on the nerve sparing procedure. Gill et al. have reported the use of intraoperative transrectal ultrasound monitoring to identify the course of the NVBs (18). With this technique, it was possible to substantially reduce the positive surgical margin rate (19).

Similar to the LRP technique, the RALP technique has also been described using the intraperitoneal or extraperitoneal approaches, but most surgeons prefer the transperitoneal approach because of larger working space and the potential for tension free urethrovesicle anastamosis. The Da Vinci robotic system (Intuitive Surgical, Inc., Sunnyvale, CA) is the only robotic platform available providing superior illumination of the surgical field. We have performed more than 250 RALPs at the Cleveland Clinic using either the transperitoneal or the extraperitoneal approach. The basic surgical principles do not differ from the LRP technique. Briefly, a 6-port strategy is used with an initially placed 12 mm port at the left superior margin of the umbilicus. Port positioning is similar for both the transperitoneal and extraperitoneal approaches (Figure-2). For the transperitoneal approach, access is achieved using the Veres needle, while extraperitoneal approach involves cut-down and dilation of the extraperitoneal space with 10 mm PDB™ System Balloon (Tyco Healthcare, Mansfield, MA, USA) which is advanced in the midline between the rectus muscle and into the retropubic space prior to inflation. The prostate is exposed, the endopelvic fascia incised bilaterally and the dorsal venous complex is oversewn with Nº.1 Vicryl suture. The bladder neck is incised and the seminal vesicles and vasa are dissected out. These are divided along with the prostatic pedicles using a harmonic dissecting scalpel. The endopelvic fascia is then reflected off the prostate preserving the NVBs. The urethra is divided and the prostate reflected cephalad. Remaining prostate-rectal fibers are divided and the prostate specimen placed in an Endocatch bag. Urethrovesical anastamosis is performed with 2/0 Monocryl and 2/0 Caprosyn sutures in a continuous running fashion.

OPERATIVE OUTCOMES

Regardless of the approach used, mortality associated with radical prostatectomy is low. The recently published reports comparing the different techniques have mainly focused on the perioperative outcomes such as OR time, estimated blood loss, analgesic requirement, length of hospitalization, duration of catheterization, and postoperative complications. Table-1 summarizes the perioperative outcomes of RRP, LRP and RALP from select large series in the published literature from pioneering centers of excellence.

In all approaches, small abdominal incision translates into low pain scores. Earlier reports suggested reduced analgesic requirements with LRP compared to RRP (8), though others reported comparable rates (20). The potential for blood loss is consistently reduced in the LRP and RALP series and is a result of the pneumoperitoneum pressure and excellent visualization. Likewise, overall complications appear to be marginally lower after LRP and RALP.

Traditionally, the duration of catheterization for RRP ranged between 2 to 3 weeks, but recent studies report shorter catheterization periods (7 to10 days). For the laparoscopic and robotic techniques, the duration of catheterization is usually in the range of 5 to 7 days. OR time appears to be shorter for RRP compared to RALP and LRP, but increasing experience with minimally invasive approaches, OR times will probably decrease.

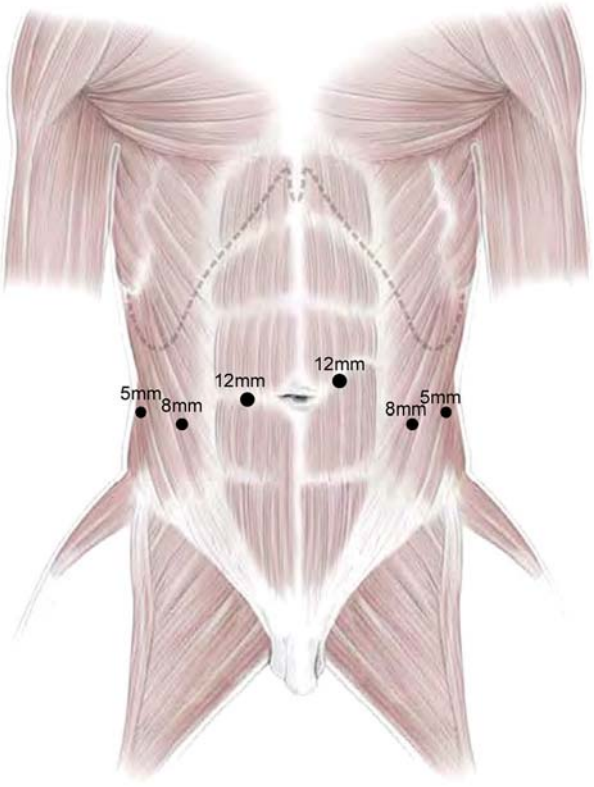

***Figure 2** – Port placement during robotic assisted laparoscopic radical prostatectomy.*

ONCOLOGIC OUTCOMES

The primary goal of prostate cancer surgery is to provide satisfactory oncologic outcomes. Although, overall and cause-specific survival rates provide the ideal measures in determining long-term oncologic control, biochemical progression and margin positivity are the two commonly used indices to assess oncologic outcomes following RRP, LRP and/or RALP. While RRP provides long-term oncologic control for up to 15 years, limited follow-up is available for the minimally invasive approaches. In patients who underwent RRP between 1998 and 2003 at the Mayo Clinic, the 3-year and 5-year PSA progression-free survival estimate rates were 99% and 98%, respectively (21). Guillonneau et al. evaluated their results in 1000 patients after LRP and reported an overall biochemical progression-free survival rate of 90.5% at 3 years (22). According to the pathologic stage, the biochemical progression-free survival rates were 92% for pT2a, 88% for pT2b, 77% for pT3a, and 44% for pT3b at a mean follow-up of 12 months. Rozet et al. reported 95% PSA progression-free survival rate at a mean follow-up of 12-months in a series of 600 patients who underwent extraperitoneal LRP (23). Rassweiler et al. reported PSA progression-free survival rates of 83% at 3 years and 73% at 5 years in 500 patients who underwent retrograde LRP (24). Patel et al. reported a PSA progression-free survival rate of 95% in 200 patients who underwent RALP with a mean follow-up of 9.7 months (25).

Table 1 *– Operative outcomes of RRP, LRP and RALP from select series.*

Institution	Technique	N of Patients	OR Time (min)	EBL (cc)	Hospital Stay (days)	Length of Catheterization (days)	Complication Rate (%)
New York University (Hsu EL et al.) (35)	RRP	1024	131	820	3.0	7 - 10	6.6
Washington University (Catalona et al.) (36)	RRP	1870	217	1395	2.4	7 - 10	10
Heilbronn (Rassweiler et al.)(8)	RRP	219	196	1550	16	12	19.1
Heilbronn (Rassweiler et al.) (8)	LRP	438	218	800	11	7	10
Montsouris (Guillonneau et al.) (37)	LRP	550	200	380	5	4.2	3.6
Cleveland Clinic (4/1999-10/2006)	LRP	759	239	303	5	8	6
Vattikuti (Menon et al.) (38)	RALP	200	160	152	1.2	7	5
Cleveland Clinic (8/2001 -10/2006)	RALP	216	199	295	1.8	8	4

Positive margin rate is another method of assessment of oncologic outcomes that is readily available giving a prediction for long-term oncologic outcome. Studies from large series demonstrated an overall positive surgical margin rate of 21- 28% for open surgery, 16.7-23.7% for LRP and 6-6.4% for RALP (Table-2).

The number of comparative studies (RRP vs. LRP vs. RALP) is limited in the literature. The true advantages and disadvantages of each technique will appear only after objective comparisons in prospective studies with long-term follow-up. DiMarco et al. noted no significant differences in positive margin rates between RRP (18.6%) and RALP (16.5%) (26). Similarly, there were no significant differences regarding the positive margin rate between RRP (19%) and LRP (22%) (27). In another study by Ahlering et al., the positive surgical margin rate was 20% for RRP vs. 16.7% for RALP (28). None of these comparative studies showed any disadvantage in terms of oncologic outcomes for the minimally invasive approaches. Furthermore, there has been no report on port site recurrence following LRP or RALP.

FUNCTIONAL OUTCOMES

Continence

Many differences exist between definitions of continence and the way that the information is obtained. The best way to analyze this outcome is undoubtedly the use of validated questionnaires. Continence rate, basically defined as requiring one or no pad per day, is reported to be between 90-92% for RRP, 82-96% for LRP and 95-96% for RALP (Table-2).

In the Prostate Cancer Outcomes Study, Penson et al. reported continence rates of 90% at 24-month follow-up and 86% at 60-month follow-up in 1288 men who underwent RRP (29). Stolzenburg et al. reported a continence rate of 84% at 6-month follow-up and a 92% continence rate at 1-year fol-

low-up in 700 extraperitoneal LRPs (30). Regarding RALP, Ahlering et al. reported a 98% continence rate at 12-month follow-up in their initial series of 200 patients (28). Moreover, Menon et al. reported a continence rate of 96% in a series of more than 1100 RALP procedures (10).

It should be noted that patient selection, tumor characteristics, and surgeon experience may interfere with the outcomes in retrospective studies. Ongoing evaluation of continence with validated questionnaires is required to compare various techniques of radical prostatectomy. Data currently available suggests that similar rates for return to continence may be achieved for the three different techniques (Table-2).

Potency

Erectile function outcomes after radical prostatectomy depend on the urologist's subjective impression, patient's self statement, use of validated questionnaires and various types of definitions for potency. Unquestionably, the performance of a nerve sparing procedure is of critical importance as well as the postoperative use of topic or oral medications.

Su et al. reported 76% of intercourse rate at 1-year follow-up after bilateral nerve-sparing LRP (31). Menon et al., in a study of more than 1100 patients, reported an intercourse rate of 64% for men younger than 60 years and 38% for men older than 60 years at 6-month follow-up (10). Table-2 outlines the potency rates for RRP, LRP and RALP from select large series in the literature. The potency rates for RRP range from 46% to 67%, 66% following LRP, and 38% to 64% after RALP from select large series in the published literature.

When the ability to perform sexual intercourse after a nerve sparing procedure was compared between the RRP and LRP, similar results, overall, were found (14). After stratifying these patients according to age and unilateral or bilateral nerve-sparing

***Table 2** – Oncologic and functional outcomes of RRP, LRP and RALP from select series.*

Institution	Technique	N of Patients	Positive Margin Rate (%)	Continence Rate (%)	Potency Rate (%)
New York University (Hsu EL et al.) (35)	RRP	1024	21	91	46
Washington University (Catalona et al.) (36)	RRP	1870	21	92	67
Heilbronn (Rassweiler et al.) (8)	RRP	219	28.7	90	N/A
Heilbronn (Rassweiler et al.) (8)	LRP	438	23.7	95.8	N/A
Montsouris (Guillonneau et al.) (37)	LRP	550	16.7	82.3	66
Cleveland Clinic (4/1999-10/2006)	LRP	759	20	96	N/A
Vattikuti (Menon et al.) (38)	RALP	200	6	96	38-64
Cleveland Clinic (8/2001-10/2006)	RALP	216	6.4	95	N/A

procedure, the rate of potency in patients younger than 55 years old undergoing LRP with unilateral nerve-sparing procedure was 36.4% vs. 36.7% for RRP. For the same group, but with bilateral nervesparing procedures, the potency rate for LRP was 77.8% vs. 69% for RRP. In patients between 55 to 65 years old with unilateral nerve-sparing procedures, the potency rate was 31% for LRP and 20.7% for RRP. In this group, but with bilateral nerve-sparing procedure, the potency rate for LRP was 60% vs. 52% for RRP. In patients older than 65 years old, the potency rates were lower, but comparable results were found for the two groups.

In a single institutional study, Abbou et al. reported similar potency rates at 3, 6, 12 months for patients undergoing RRP and LRP (32). To date, there are no comparative studies that show inferior results in terms of potency for LRP compared to RRP. However, it is important to remember that these comparative studies are limited to different patient characteristics and sample sizes.

COST CONSIDERATIONS

In the era of minimally invasive approaches, the economic issues are important. Lotan et al. reported that RRP had a cost advantage of $487 over LRP and $1726 over RALP (33). The cost difference is specifically based on the price of a 1.2 million dollar Da Vinci robotic system (the original system) with a maintenance fee of $100.000 per year (34). There are three robotic systems currently available. The original three-arm system, the four-arm system (approximately 1.4 million dollar) and the new "S-model" (approximately 1.6 million dollar) and high-definition (additional cost) sub-models, each with different purchasing and maintenance costs (maintenance costs are approximately 10% of the purchasing cost). The additional cost of disposables is approximately $2,000 US/case. This is of extreme importance as costs are one of the main factors institutions take into consideration when acquiring new technologies.

The economics of radical prostatectomy in Europe differ from the USA, because of different hospitalization mentality (patients usually stay in the hospital until the urinary catheter is removed in Europe) (24). Using this methodology LRP represented a cost saving of $1237 per case compared to RRP and this is attributed to the reduced hospitalization with LRP (6 days) compared to RRP (8 days) (8).

Although RRP is considered the least expensive at present, LRP related expenses have significantly decreased, which could lead soon, to cost equivalence to RRP. On the other hand, the RALP technique will certainly need a substantial decrease in the cost of the robotic system and other relevant robotic instruments as well as maintenance fees in order to achieve wider global acceptance and application.

The advantages and disadvantages of RRP, LRP and RALP are detailed in Table-3.

CONCLUSIONS

Despite only intermediate term follow-up being available for LRP and RALP techniques, current available data demonstrates that laparoscopic and robotic prostatectomy procedures achieve oncologic and functional outcomes similar to the well established technique of open radical prostatectomy. Indeed, in most studies, better results are achieved with LRP and RALP in terms of blood loss, convalescence and cosmetics when compared to RRP.

However, LRP is associated with a steep learning curve and longer operative time. The RALP technique holds potential for better ergonomics. The initial purchase and maintenance fees for the robotic platform are still expensive. Efforts to reduce the cost for RALP must be materialized for this technique to compete with others worldwide.

After intermediate term follow-up, LRP and RALP techniques have already gained wider acceptance in the treatment of localized prostate cancer. With an expected reduce in the cost and decrease in the learning curve and OR time, minimally invasive prostatectomy techniques have the potential to be the gold standard in the treatment of localized prostate cancer worldwide. However, long term data and adequately designed comparative studies are clearly needed to assess the inherent advantages and disadvantages of the three different techniques.

Table 3 *– Advantages and disadvantages of RRP, LRP and RALP.*

	RALP	LRP	RRP
Advantages	- Decreased blood loss - Faster recovery - Better cosmetic results - Decreased hospital stay - Enhanced visibility of vital structures (i.e. NVB) - Superior ergonomics for the primary surgeon - Shorter learning curve compared to LRP	- Decreased blood loss - Faster recovery - Better cosmetic results - Decreased hospital stay - Enhanced visibility of vital structures (i.e. NVB) - Lower cost compared to RALP	- Proven oncological outcomes - Tactile feedback - No additional training required
Disadvantages	- No long-term oncological data - High initial and procedural cost - Longer operative time - Limited instrumentation	- No long-term oncological data - Steep learning curve - Longer operative time	- Increased blood loss - Increased length of catheterization (historical series)

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

The authors compare oncologic, functional and cost outcomes between open radical retropubic prostatectomy and the two laparoscopic approaches: pure and robotic-assisted.

They conclude that all outcomes are similar with the exception of costs, which are greater with the use of robotic-assistance. Currently, robotic technology is almost universally available in the United States. This availability has allowed many urologic surgeons to venture into the field of advanced laparoscopic surgery. Robotic technology is also available in many centers in Europe. Nevertheless, several well-established groups continue to perform pure laparoscopic surgery as they have achieved a high level of experience. This experience allows them to perform the surgery with the same oncologic and functional outcomes as with the ones reported with the use of robotic-assistance. Conversely, in Latin America, the majority of laparoscopic prostatectomies are performed by the pure laparoscopic approach due to the lack of access to robotic technology.

This well structured review should be a tempering reminder that, as of present, the reported outcomes for surgery are the same regardless of the approach. The importance of the learning curve and experience in achieving maximal oncologic and functional outcomes should always be remembered. There are currently competing, effective treatments for localized prostate cancer such as the different forms of radiation therapy, cryotherapy, and high intensity focus ultrasound. Therefore, it is incumbent upon the urologic surgeon to remain abreast of improvements in technique, advances in technology and to maintain maximal surgical skills regardless of the approach.

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EDITORIAL COMMENT

For patients diagnosed with prostate cancer, choosing whether and how to treat can be a daunting task. The widespread implementation of minimally invasive surgical approaches has dramatically altered the landscape of treatment options. Short-term perioperative benefits from laparoscopic and robotic-assisted surgery have been definitively established. However, in regard to more meaningful outcomes such as cancer control, urinary continence, and sexual function methodologically sound comparisons to open surgery are lacking (1).

Recognizing the inherent limitations in the published literature (e.g. patient selection, tumor characteristics, and surgeon experience), the authors do an excellent job of concisely and evenhandedly reviewing the three most common surgical approaches to radical prostatectomy. In light of the multiple options, we agree the impact of surgeon skill and experience is likely to be far more important than whether he or she looks at the prostate on a television monitor or via an open incision (2-5).

Further, an honest understanding of the merits and limitations of the individual procedures will only be garnered when validated questionnaires are uniformly used to assess functional recovery and quality of life. The inconsistent use of these metrics coupled with the potential for selection bias skews the available data and accounts for the wide range of reported outcomes.

The percentage of radical prostatectomies performed laparoscopically or robotically has been steadily increasing, from 12% to 31% between 2003 and 2005, and will likely continue to do so (4). However, we must be careful of "gizmo idolatry" and beware of the trap of "the cutting edge or first on the block use of a gizmo" which can "bestow on the physician a mantle of expertise, competence, and pre-eminence even if there is little or no evidence that the patient will benefit" (6). Careful, honest, and diligent review of outcomes, as this and other studies undertake, will be of utmost importance to ensure that we are offering patients the optimal treatment and not just the latest gizmo.

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Fluoroscopy Guided Instillation Therapy in Chyluria Using Combination of Povidone Iodine with Contrast Agent. Is a Single Instillation Sufficient?

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ABSTRACT

Purpose: To evaluate the safety and efficacy of a single instillation in a combination of povidone iodine with contrast agent under fluoroscopy guidance for the treatment of chyluria.

Materials and Methods: From December 1999 to July 2006 a total of 40 patients with chyluria were treated by renal pelvic instillation therapy (RPIS). The sclerosing solution was prepared using povidone iodine with contrast agent diluted with sterile water in a ratio of 1:1:3. It was instilled on the side having chylous efflux using a bulb tip ureteric catheter. Unilateral instillation was done in 26 cases, 10 on the right side and 16 on left. Fourteen patients had bilateral chylous efflux and RPIS was performed on both sides in the same session. Fluoroscopy was used to evaluate the complete filling of the pelvic calyceal system. The sclerosing solution was kept in the system for 5 minutes and the ureteric catheter was then withdrawn.

Results: Immediate clearance was observed in 39 patients. Recurrence occurred in five patients. They were treated again using the same procedure with satisfactory results. The longest follow-up was five years and the shortest five months.

Conclusion: RPIS of chyluria using a single instillation a combination of povidone iodine with contrast agent is safe and effective. Use of fluoroscopy helps to determine the exact amount of sclerosing solution required to completely fill the system and therefore overfilling is avoided. Moreover, the complications, which arise due to pyelointerstitial backflow, are prevented.

Key words: *chyle; chyluria; povidone iodine*

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INTRODUCTION

Chyluria is basically a urological manifestation of lymphatic system disease, occurring as a result of communication between the lymphatics and renal pelvis (1). Although not life threatening it often causes morbidity due to its presentation like hematochyluria, colics, etc. It also leads to nutritional deficiency and a state of compensated immunosuppression (2). Chyluria is a condition with spontaneous remissions and exacerbations. Treatment with high protein and low fat diet is effective in some patients whereas antifilarial drugs are not helpful in this late manifestation of parasitic infestation by Wuchereria bancrofti (3). The treatment most frequently used is renal pelvic instillation sclerotherapy (RPIS) to cause sclerosis of pyelo-lymphatic fistulae. Various sclerosants like silver nitrate in varying concentrations of 0-1% - 3%, povidone iodine 0.2%, sodium iodide 15-25%, potassium bromide 10-25%, dextrose 50%, hypertonic saline and meglumine diatrizoate (Urograffin76% Schering Pharm, Germany) have been used (4-10).

Although silver nitrate enjoys wide popularity and has a success rate of 68-80%, its preparation

involves several steps subject to human error. It can also be associated with side effects like flank pain, nausea, vomiting, interstitial nephritis, chemical cystitis, papillary necrosis, arterial hemorrhage, pelviocalyceal cast formation, ureteric strictures, acute renal failure. Moreover, even death has been reported with its use (4,10-14).

In the search to obtain an efficacious but less toxic and safe alternative povidone iodine has been used (7-9). It has been used either as a single instillation of 8-10 mL of diluted solution (7) or as 8 hourly instillation of total 9 doses (8) or in combination with 50% dextrose twice a day for 3 days (9).

We have studied the combination of povidone iodine with contrast agent as a single instillation using fluoroscopy to determine the exact amount of sclerosing solution needed.

MATERIALS AND METHODS

From December 1999 to July 2006, 40 patients (24 males, 16 females) were treated for chyluria. The majority of patients were in the 20-30 year age group (Table-1). All patients presented with a previous history of passage of milky white urine. The duration of symptoms ranged from eight years to four months. The associated symptoms were hematuria in 17, flank pain in five, dysuria in three, fever in three and passage of chylous clots in 11 patients. One patient had previously undergone RPIS using silver nitrate but had no relief from symptoms.

The diagnosis of chyluria was made by the ether test in all patients. Abdominal ultrasound was done as part of the protocol in all patients. It did not show any abnormality in any patient. Intravenous urography was carried-out in the first 12 patients and was essentially normal. Pyelo-lymphatic communication was not observed in any of the patients on intravenous urography. Sixteen patients had previously received a course of diethylcarbamazine. Those who had not received the course were started on diethylcarbamazine.

All patients underwent cystoscopy under general anesthesia. They were asked to include some butter in their meal the night before the procedure. This was very helpful in localizing the side of chylous efflux. In 26 cases the chylous efflux was unilateral; 10 on the right side and 16 on the left side. The efflux was observed bilaterally in 14 patients. All the sides showing chylous efflux were subjected to RPIS.

The sclerosant solution was prepared by using povidone iodine 5%, contrast agent (Urograffin 76%, Schering Pharm, Germany) and sterile water in the ratio of 1:1:3. A bulb tip (Chevassu) ureteric catheter was used to instill the sclerosant in the pelviocalyceal system. Imaging in the form of C-arm fluoroscopy was used in all patients to visualize the complete filling of the pelviocalyceal system. The system was filled until blunting of all fornices was seen. Thus, over distension of the system and the consequent risk of pyelointerstitial backflow of the sclerosing solution was avoided. The ureteric catheter was kept at the ureteric orifice to prevent the sclerosant from being drained in the bladder. The other end of the ureteric catheter was blocked to prevent the sclerosant from dripping out. The sclerosant remained in the system for five minutes and then the ureteric catheter was removed.

In patients with bilateral chylous efflux both sides were treated in the same session.

In the course of follow up serum creatinine was evaluated in those who had undergone bilateral RPIS. Intravenous urography was done after one month in the first five patients but was not done in the subsequent patients.

Table 1 *– Age distribution.*

Age (years)	**N of Patients**
< 20	1
20 - 30	20
30 - 40	14
> 40	5

RESULTS

Of the 40 patients, all, except one patient, had immediate clearance of urine. In one patient the chyluria persisted for two days after RPIS but subse-

quently the chyluria stopped and the patient was free from symptoms at a follow up of five months.

There was recurrence of chyluria in five patients. One had recurrence after one month, two patients had recurrence after three months and another two patients had recurrence after six months. All were retreated using the same procedure as described above. No relapse was noted after re-treatment.

The patient who had a previous RPIS using silver nitrate did not show any recurrence after RPIS using povidone iodine with contrast agent.

The post treatment period was uneventful in all patients except for minimal pain and dysuria in some cases. Post treatment intravenous urography was done in only in five patients. Three of them had undergone bilateral RPIS. It was found to be normal in all patients. In view of this finding and the minimal theoretical risk of renal damage or ureteric strictures using this technique and sclerosing agent, subsequent patients were not subjected to intravenous urography. Serum creatinine was normal in the follow-up studies of all patients who had undergone bilateral RPIS.

None of the patients, except the five mentioned above, had recurrence during the follow up. This was confirmed by examining the urine by the ether test. The longest follow-up was five years and the shortest was five months. The average follow-up is one year.

COMMENTS

Chyluria usually affects the lower socio-economic class and is not uncommon in India, China, Japan, Taiwan, Africa or in South East Asian countries (15). Although a variety of parasitic and non-parasitic causes can cause chyluria, it is generally agreed that it should be considered as filarial unless proved otherwise, particularly in areas where lymphatic filariasis is or was endemic (16). Non-parasitic causes such as malignant tumors of the thoracic duct, pregnancy, trauma etc. are rare (6).

Parasitic infection causes obstruction to the retroperitoneal lymphatics leading to dilatation, proliferation and subsequent rupture of the lymphatics into the pelviocalyceal system (15). Recent observations suggest that the extensive lymphangiectasia observed in Bancroftian filariasis is secondary to lymphatic dysfunction caused by cytokines liberated by adult filarial worms and by the host immune responses to the parasite (17,18).

The diagnosis of chyluria can be made by observing the urine sample and by doing the ether test (4,6). Goel et al. found lymphocyturia a more sensitive tool to diagnose chyluria than the ether test (8). In the present study all patients with suspected chyluria had a positive ether test. Lymphocyturia was not evaluated in any of the patients. Additional tests to localize the pyelo-lymphatic communications, like lymphangiography and Intravenous Urography, are neither found to be useful nor cost effective (4,5). We did not carryout a lymphangiography in any of the patients. Those patients who had an IVU did not show any pyelo-lymphatic communication.

Chyluria is debilitating and causes morbidity but is not life threatening . Hence the treatment of chyluria should be safe, effective and minimally invasive. RPIS has been considered the most popular form of treatment. The basic principle is to instill a sclerosant in the renal pelvis so that it can enter the pyelo-lymphatic communications and induce an inflammatory reaction. This chemical lymphangitis leads to edema of the lymphatic channels and the resultant blockage leads to immediate relief. Subsequent healing by fibrosis results in permanent remission (4).

The most commonly used sclerosant is silver nitrate. It has been used in concentrations ranging from 0.1% to 3% and instilled using varying protocols ranging from a single instillation up to as many as nine instillations over 3 days (4-6,19). Dalela et al. have found that three instillations performed every eight hours in a single day are as effective and associated with less morbidity as compared to nine instillations done every eight hours over three days (19). However, the use of silver nitrate has its share of problems. It is water insoluble and susceptible to light. The solution needs to be freshly prepared and autoclaved. Evaporation of water in the autoclave may alter the concentration of the solution (8). Most patients complain of nausea, vomiting, flank pain and hematuria (4). Anaphylactic reactions, ureteric strictures and severe chemical cystitis are known to occur with its use (10). Even death has been reported following bilateral RPIS using 3% silver nitrate (14).

In addition, there is a significant failure rate ranging from 22-30% (5,6).

In the search to achieve a more safe and effective sclerosant various substances have been used. Povidone iodine has been recently evaluated either alone or in combination with 50% dextrose solution (7-9). It is an iodine complex with the non-ionic surfactant polymer polyvinylpyrrolidone. It is also water-soluble and releases iodine slowly. This procedure provides a non-toxic, non-irritating, non-volatile and non-staining form of iodine. It exerts a local sclerosant action and has antibacterial, antiseptic *a*nd antifungal properties. Moreover, it is inexpensive, easily available and can be easily diluted to the required concentration. Shanmugam et al. treated five patients with a single instillation of 0.2% solution prepared by diluting 5% povidone iodine with distilled water in the ratio of 1:5. All their patients were free of symptoms at six months follow-up (7). Goel et al. performed eight hourly instillations of 0.2% povidone iodine, to a total of nine doses. They first assessed the renal pelvic volume by retrograde pyelography and then accordingly instilled the sclerosing solution in volumes varying from 6-10 mL with the patient in Trendelenburg position. These authors had recurrence in 22% of patients and found povidone iodine as effective as silver nitrate (8). Nandy et al. used a combination of 5 mL povidone iodine with 5 mL of 50% dextrose, which was instilled twice a day with the patient in Trendelenburg position for 3 days. They had complete remission in 87%, persistence in 13% and noted recurrence in 2 out of 47 patients (9). In all of these studies bilateral instillation was not performed during the same sitting.

These studies demonstrate that povidone iodine is associated with satisfactory results in the treatment of chyluria. In addition, meglumine diatrizoate (Urograffin 76%) has been used for RPIS (10). We have studied the efficacy of a combination of 5% povidone iodine with contrast agent (Urograffin 76%) diluted with sterile water in a ratio of 1:1:3. This ratio was arbitrarily decided and as it initially produced good results. . As fluoroscopy was used during the procedure with a contrast agent the pelviocalyceal system was well delineated. The most common site of lymphatic-urinary communication is at the fornices; hence the sclerosing solution was instilled until the blunting of all fornices was seen. Thus the chances of overlooking any fistulae were minimized. In addition, the instillation of the sclerosing solution was stopped once all the fornices were blunted. Over distension of the pelviocalyceal system, with its associated risk of pyelointerstitial and pyelo-venous backflow, was thus avoided. Shanmugam et al. used a single instillation of 8-10 mL of diluted povidone iodine (7). As the capacity of the pelviocalyceal system varies from each individual it is only logical that the amount of sclerosing solution needed to optimally fill the pelviocalyceal system could vary from patient to patient. Prior retrograde pyelography can determine the exact pelvic volume. Considering these facts we have combined contrast agent with povidone iodine. By using fluoroscopy we can visualize the complete filling of the system. In addition, the iodine content of the contrast agent helps to enhance the sclerosing efficacy of the solution. This is supported by the fact that good results were obtained by other investigators when contrast agents alone were used (10).

The optimum time for which sclerosing agent should be in the pelviocalyceal system is not known but it should be long enough to induce chemical lymphangitis and edema of lymphatic channels. Most of the investigators have used from three to nine instillations for RPIS (4,5,8,9). In our study we instilled the sclerosing solution using a bulb tip ureteric catheter and once the system was optimally distended, blocked the end of the ureteric catheter and kept it at the ureteric orifice to prevent the sclerosing solution from effluxing out of the system. The sclerosing solution was kept in the system for five minutes. Whether keeping the solution in the collecting system for a lesser period of time will produce the desired result may be answered by a separate study.

We had a success rate of 87.5% using a single instillation. This was comparable with the results of the two other series using povidone iodine where the sclerosing solution was instilled either thee times or twice a day over a three day period. There was recurrence in only five patients who were treated again with satisfactory result. In one patient the chyluria persisted for two days and then cleared. We feel that this could have been caused by delayed occurrence of edema due to the chemical lymphangitis. The patient was free from chyluria at a follow-up of five months. The procedure was well tolerated by all patients who

participated in the study. There was minimal pain. No major side effects or complications were observed. The procedure was done bilaterally in 14 patients in the same sitting with no side effects. The incidence of bilateral chylous efflux was higher in our study however we could find no particular explanation for this occurrence.

CONCLUSION

The authors suggest that the use of a combination of povidone iodine with contrast agent is safe and effective for the RPIS of chyluria. Fluoroscopic guidance helps to optimally fill the pelviocalyceal system. Thus under filling of the system is avoided and the chances of resultant failure of the therapy are minimized. In addition, as overfilling of the system does not occur and the complications due to pyelointerstitial and pyelo-venous backflow are prevented. This would otherwise occur if the sclerosing solution were instilled in random amounts exceeding the capacity of the pelviocalyceal system.

In this study a single instillation was as effective as multiple instillations done by other investigators. This also reduced the need for prolonged hospitalization of the patients.

A drawback of this study is the absence of a control arm and a relatively short follow up in majority of the patients. However, our results in fact suggest that this particular form of RPIS using fluoroscopy for the instillation of a combination of povidone iodine with contrast agent is safe, inexpensive, effective, minimally invasive and is associated with a short hospital stay. Also the procedure can easily and safely be reapplied in patients with recurrence.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

The authors have instilled a mixture of povidone iodine and meglumine diatrizoate in the involved pelviocalyceal system using a bulb tipped ureteric catheter. While the collecting system is being filled it is monitored fluoroscopically to achieve a so-called 'completely full' system. The bulb of ureteric catheter is intended to keep the ureter 'completely' occluded for 'five minutes'. The authors claim that by using this methodology they prevent overfilling of system and thus the pyelointerstitial back flow and its consequences are avoided.

This claim appears to be more of a conjecture because during the period of five minutes while the ureter is occluded by bulb tipped ureteric catheter, the kidney will continue to produce urine, which, at least theoretically, may blowup the system and open up pyelointerstitial/pyelo-lymphatic backflows.

Nevertheless, it is the first report on use of povidone iodine with contrast media. To date, the problem of best dose, best concentration and no. of instillations remains vexed. Controlled studies are needed to clarify the same.

Recent reports have generated interest in the role of doxycycline as a drug to reduce the pathology of lymphatic filariasis (1). Its applicability to patients with chyluria needs to be locked into.

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EDITORIAL COMMENT

Sclerotherapy, that is a minimally invasive treatment modality, is justified once conservative modalities fail. Different investigators have used many sclerosants in different concentrations. However, the maximum experience has been with silver nitrate. Because of the various problems associated with silver nitrate, recently there has been shift and many urologists have started using povidone iodine. The results of chyluria are mostly evaluated based on patient's history of any recurrence of milky urine (which may be associated with pitfalls like under or over reporting). In the study reported by Sharma et al, the authors have not mentioned the follow-up protocol. In all probability, it is also based on the patient's evidence of milky urine. It would be interesting to see if the disease also responds completely biochemically. Estimation of urinary triglycerides is considered 100% sensitive and specific test for chyluria (1). It is noninvasive and cost effective and is independent of manual error. Whether chyluria is continuous/intermittent, mild or severe, urinary triglycerides are invariably detected in morning samples (2). Estimation of urinary triglyceride levels pre- and post- instillation of sclerosants may also give insight about the patients who are likely to recur. Follow-up of patients of chyluria is extremely difficult. If we can predict recurrence based on biochemical triglyceriduria then it may help us in designing better therapy for this problem.

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Intravesical Anesthesia for Bladder Tissue Biopsies. Comparison of Two Methods

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ABSTRACT

Purpose: To estimate the level of analgesia which can be obtained with simple intravesical instillation of ropivacaine in comparison to the combination of both instillation and subepithelial injection of the same agent.
Materials and Methods: Fifty-two patients were randomized in order that half (26) of them received simple intravesical instillation of ropivacaine (100 mL solution of ropivacaine in a concentration of 2 mg/mL) (Group A), whereas the other 26 patients received both intravesical instillation and subepithelial injection of 2 mL (4 mg) at the site of biopsy (Group B). In both groups, tissue samples were obtained from urinary bladder (number of biopsies from 3 to 4). The pain during the procedure was estimated by using the Visual Analogue Scale (VAS) which ranged from 0 to 10.
Results: The entire procedure was integrated with success in 50 out of 52 patients. The VAS score for the Group A ranged from 4 to 6 (mean 5.08), whereas for Group B from 1 to 3 (mean 1.6). ($p < 0.0001$). Higher values of VAS score were recorded in males in both Groups ($p < 0.05$). When complications of this method produced a slight bleeding (hematuria) in 6 patients (2 from group B and 4 from group A), they were treated with oral administration of fluids. Allergic reactions were not recorded. Hospitalization did not exceed 3 hours after the procedure.
Conclusions: The analgesic effect that was obtained with the combination of intravesical instillation and subepithelial injection of ropivacaine provides a safe method of anesthesia for transurethral bladder biopsy.

Key words: *bladder, local anesthesia, ropivacaine, biopsy*
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INTRODUCTION

The biopsy of the urinary bladder is a minimally invasive procedure, which is commonly employed for detection of urinary bladder pathology (such as carcinoma in situ, interstitial cystitis, etc).

Several studies suggest that the analgesia, which can be obtained with intravesical instillation before transurethral biopsy of the urinary bladder, may offer an acceptable level of analgesia, although this procedure does not totally eliminate patient's complaints by using this method (1-5).

The aim of this pre-emptive study was to attempt to estimate the analgesic effect during the biopsy procedure, which may be administered by either the simple instillation of ropivacaine or the combined instillation and subepithelial injection of the same agent. A comparison between the two methods was accordingly performed.

MATERIALS AND METHODS

Fifty-two randomized patients (30 male, 22 female) with an age range 25-86 (mean 56.42) were

enrolled in this study. All patients were fully informed regarding both the procedure and the type of analgesia and provided their written consent, which was formulated according to local legislation.

The patients were randomized so that 50% of them (16M, 10F) received simple intravesical instillation of ropivacaine (Group A) whereas the other 26 patients (14M, 12F) received both intravesical instillation and sub epithelial injection at the site of biopsy (Group B). Cup biopsies were performed for histopathologic examination of suspicious for non-exophytic neoplasia areas of bladder urothelium, mainly carcinoma in situ (CIS).

In each patient intraurethral lubrication with lidocaine hydrochloride 2% gel was performed before the procedure. Then, a 10F Nelaton catheter was used for intravesical instillation of 100 mL solution of ropivacaine (2 mg/mL), 30 minutes before the biopsy.

In the endoscopic operation room of our department a diagnostic cystoscopy was performed using a 24F rigid endoscope (Karl Storz). In the Group A, biopsies were obtained in a straightforward manner using grasp forceps. In the Group B a flexible metal needle (Karl Storz 27184A) was inserted through the working channel of the rigid endoscope. After the detection of the suspicious area, submucosa injection 2 mL of ropivacaine 2 mgr/mL was performed taking care to avoid bleeding of the area, which subsequently was biopsied with grasp forceps (cup biopsy). In both groups biopsies were from 3 to 4.

Each patient was asked to estimate the severity of pain during the procedure using the Visual Analogue Scale (VAS) from 0 to 10 and remained in the Urology Department for a short-term observation.

The VAS values and the gender of each patient were recorded. Statistically significant differences ($p < 0.05$) between the VAS values between the two Groups were analyzed based on the type of analgesia and the gender, using the Student's-t-test for independent samples (two tailed).

RESULTS

The entire procedure was integrated with success in 50 out of 52 patients. In 2 patients the procedure was not completely performed due to poor endoscopic conditions (low visibility caused by prostate bleeding in the presence of enlarged prostate). One of these patients was in Group A and one in Group B.

The VAS score for the Group A ranged from 4 to 6 (mean 5.08), whereas for the Group B from 1 to 3 (mean 1.6) ($p < 0.0001$). In each group (A and B), the VAS values were significantly higher in men than in women of the same Group ($p = 0.0005$ and $p < 0.0001$, respectively) (Table-1). Statistically significant difference ($p < 0.0001$) was observed in VAS values depending on gender between the two groups (Table-1).

There was no systemic adverse effect from ropivacaine. Due to complications of this method, a slight bleeding (hematuria) occurred in 6 of 50 patients (2 from Group B and 4 from Group A), which was resolved using oral administration of water. Allergic reactions were not recorded. Hospitalization never exceeded 3 hours after the procedure.

COMMENTS

Minimally invasive techniques are employed in routine urological surgery with increasing frequency, possibly due to the demand for treating patients by one-day surgery. The employment of local anesthesia offers a large variety of benefits such as the patient's safety (2,5,6), minimal hospitalization, the reduction of any complications associated with general or epidural anesthesia and the low cost (4,6,7).

Although pain is a subjective symptom, the employment of the VAS score was used for the purpose of this study in order to estimate, as objectively as possible, this reaction in our patients (from slight discomfort to severe pain).

The intravesical instillation of a local anesthetic was initially described in 1991 (1,2) and since then many authors have followed the same practice, as referred in many studies. Although the administration of lidocaine by EMDA technique offers effective anesthesia at the level of urothelium (8,9), it is a rather sophisticated method. Intravesical instillation is safe, since the levels of Lidocaine are significantly much lower as regards the toxic levels, even if the technique is employed on denuded urothelium and almost totally

Table 1 – *Number of patients, visual analogue scale (VAS) values, mean VAS values and statistical differences between the groups.*

	N	**Sum - VAS**	**Mean - VAS**	**p Value** (two tailed)
Group A	25	127	5.08	< 0.0001
Group B	25	40	1.6	
Group A (men)	16	87	5.43	0.000563
Group A (women)	9	40	4.44	
Group B (men)	14	29	2.07	< 0.0001
Group B (women)	11	11	1	
Group A (men)	16	87	5.43	< 0.0001
Group B (men)	14	29	2.07	
Group A (women)	9	40	4.44	< 0.0001
Group B (women)	11	11	1	

harmless whenever the technique is employed on intact urothelium (1-3,5,10). In addition to lidocaine, other local anesthetics such as bupivacaine have been employed either intravesically or as subtrigonal injection (6,11,12) without any adverse effects.

Ropivacaine is the pure S (-) enantiomer of N-propyl-2'6-pipecoloxylidide and created from the need to produce a local anesthetic effective over a long period without any cardio toxicity which is, although very rarely the case , associated with bupivacaine. Ropivacaine prohibits both the initiation and the transmission of neural signals by reduction of membrane permeability of the neural cell in Na+. The consequential arrest of depolarization leads to conductibility arrest. Small neural fibers are more sensitive to this effect and therefore demand a longer period of rehabilitation. The sensory fibers of pain are the first that are usually blocked. The extension of anesthesia depends on the diffusion of the solution, which is mostly affected by the area where this solution is administered and by the amount of the administered solution (13). To our knowledge, it is the first time that ropivacaine was employed for both local intravesical and submucosa anesthesia of the bladder. The concentration of 2 mg/mL was empirically selected in this study.

In addition, although the employment of the submucosa injection of a local anesthetic has proved efficacious for transurethral resection of superficial bladder tumors (6) and the intravesical instillation of similar agents have been used for minimal transurethral operations (14-16), this is the first time that a combination of both techniques was performed.

As clearly demonstrated in our study by the difference in VAS values between the two groups, the injection of ropivacaine by needle at the biopsy site combined with the intravesical instillation of the same agent offers greater reduction of pain than simple instillation of the same agent. Therefore, it is clearly suggested that the submucosa injection improves the analgesic effect of a local anesthetic, which was previously instilled into the urinary bladder. The superiority of the combined technique (intravesical instillation plus submucosa injection) as compared to simple instillation may be attributed to the prohibition

of signals from sensory receptors to the centripetal C fibers, which form a submucosa network at the bladder wall. This network is responsible for activation of detrusor muscle. The action of local anesthetics, as has been proved recently, is not limited only to sensory fibers but extends to the centrifugal neural fibers and to the detrusor muscle, although this extended action demands higher concentrations (17).

Male patients experienced more pain than women possibly due to the differences in the anatomy of the lower urinary tract between two sexes, such as already mentioned by others (18).

Our method is easily applicable and safe. All cases were performed on an outpatient basis. The slight hematuria in a small number of patients subsided soon after the procedure and was mostly attributed to the effect of tissue resection from biopsy and not to the puncture of bladder wall for injecting the local anesthetic.

Furthermore, our results suggest that the analgesic effect of the combination of both submucosa injection and intravesical instillation (mean VAS value 1.6 in a 10-scale VAS) might be similar to the analgesic effect of caudal anesthesia during transurethral biopsies of urinary bladder with forceps (mean VAS value 0.8 in a 5-scale VAS) (5). Therefore, if our observation is confirmed in a larger number of patients, any type of anesthesia could be replaced by this method, whenever there is a need for bladder biopsies or, at least, in patients who are at high risk for other types of anesthesia.

CONCLUSIONS

Transurethral biopsies of the urinary bladder can be performed with high level of analgesia whenever the combination of intravesical instillation and submucosa injection of ropivacaine is employed. The analgesic effect of this combination could be similar to caudal anesthesia and significantly superior as compared to simple instillation. Therefore, the intravesical instillation and the simultaneous submucosa injection of ropivacaine can safely replace caudal or general anesthesia and their subsequent morbidity when there is need for urinary bladder biopsies or any other minimal invasive transurethral procedure of the urinary bladder.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

Transurethral biopsy of the bladder lesion is an office-based procedure. Although this procedure is minimally invasive and most of the patients can tolerate the bladder biopsy without any anesthesia, pain associated with the biopsy is still a matter that urologist should take into consideration. This study reported the results comparing the VAS responses of patients receiving intravesical and combined intravesical and suburothelial ropivacaine anesthesia for bladder mucosa biopsy. The results showed that combined anesthesia offers remarkable anesthetic action than intravesical anesthesia alone. A higher VAS score was reported in patients with intravesical anesthesia alone and in male patients of both procedures.

Recent investigations have shown that suburothelial space is rich in sensory nerve plexus. Many sensory receptors and neuromediators such as calcitonine-gene related peptides and nerve growth factor may contribute to the perception of bladder pain or activation of detrusor overactivity. Although intravesical instillation of anesthetic agent can provide anesthetic effect, the drug might not penetrate into the deep suburothelial space. Local anesthesia injects anesthetic agent into the deep suburothelial space and even the underlying muscle layer, which may eliminate bladder pain during biopsy procedure. Therefore, the results of this study seem to be expected because double anesthesia should be better than intravesical anesthesia alone. It will be interest-

ing to know if intravesical anesthesia offers significant pain relief than no anesthesia, or local anesthesia with ropivacaine alone which has a similar effect when combined anesthesia. If local anesthesia alone is as effective as combined intravesical and local anesthesia, intravesical anesthesia might not be necessary in performing this minor bladder procedure.

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EDITORIAL COMMENT

In the management of superficial bladder cancer and carcinoma in situ, it is important to biopsy suspicious lesions in order to confirm or reject the existence of epithelial abnormalities. We have performed such procedures under general or spinal anesthesia where the patient was hospitalized. The authors have performed a randomized controlled study to investigate the efficacy of two different methods, intravesical instillation of ropivacaine and combination of both instillation and subepithelial injection of ropivacaine for patients who underwent a transurethral bladder biopsy in an outpatient basis and concluded that the combination is significantly better than the instillation alone.

As described by Taghizadeh et al. (references 18 in article), it has been demonstrated that the most painful part of flexible cystoscopy is when the tip of the cystoscope passes through the external sphincter. If it is compared in women only in this study in order to eliminate the effect of pain for lower urinary tract, it has been demonstrated that the combination is significantly better than the instillation alone however the number of patients in this study is small. Therefore, the combined intravesical and local anesthesia of ropivacaine for bladder biopsy might be able to replace caudal and general anesthesia with lower cost. However, this may be inadequate for lesions large enough to require resection rather than cold cup biopsy and those patients with poorly accessible regions of the bladder. Further studies are required to evaluate the cause of pain for bladder biopsy in order to perform better local anesthesia.

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Histopathological Findings in Extended Prostate Biopsy with PSA ≤ 4 ng/mL

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ABSTRACT

Objective: Cancer detection has been reported in up to 27% of patients when lowering the PSA cutoff to 2.5 ng/mL. Although this practice could increase the number of biopsies performed, it also could lead to more frequent detection of significant prostate cancers at an organ-confined stage and/or a less aggressive state. This study describes the incidence of malignancy and tumor characteristics in extended prostate biopsies with PSA ≤ 4 ng/mL.
Materials and Methods: Prostate biopsies from 1081 patients where examined, 275 (25.4%) patients had PSA level ≤ 4 ng/mL.
Results: Cancer was diagnosed in 32.0% and 35.7% of patients with PSA ≤ 4 ng/mL and > 4 ng/mL, respectively (p = 0.906). The median Gleason score was 7 independent of PSA > or ≤ 4 ng/mL (p = 0.078). The median number of cores positive for tumor was 4 and 3, respectively, for PSA > 4 ng/mL and PSA ≤ 4 ng/mL (p = 0.627). There was a difference in the total percent of tumors involving all cores, 11% and 7% for PSA > or ≤ 4 ng/mL (p = 0.042). Fifty-six patients underwent radical prostatectomy, 12 had PSA ≤ 4 ng/mL. In both groups, a diagnosis of cancer was accurate with no differences in Gleason score, tumor volume or staging for both groups.
Conclusion: When PSA is below 4 ng/mL, cancer is detected in a proportion equal to the proportion diagnosed with a PSA > 4 ng/mL, and tumor characteristics are similar between the two groups. Only clinically significant tumors were diagnosed following radical prostatectomy.

Key words: *PSA; prostate cancer; biopsy; diagnosis; Gleason score; tumor volume*
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INTRODUCTION

Numerous investigators have demonstrated the detection of an increasing proportion of early-stage prostate cancer (CaP) and improvement in biochemical outcome after treatment in the Prostate-specific antigen (PSA) era (1-4). It is also believed to be at least partially responsible for the recent decline in prostate cancer mortality rates in the US and in some European countries (5,6).

Traditionally, a PSA cutoff of 4.0 ng/mL has been used to recommend prostate biopsy (7). However, one third of men with PSA level between 4 and 10 ng/mL and more than one half with PSA greater than 10 ng/mL are found to have cancer that has extended to the surgical margins or to the extraprostatic tissue (8).

When the PSA cutoff level is lowered to 2.5 ng/mL, the cancer detection rate has been reported to be up to 27%. Although a PSA threshold of less

than 4.0 ng/mL may increase the number of biopsies performed, studies have shown that it also leads to more frequent detection of significant CaP at an organ-confined stage and/or a less aggressive state with no excessive increase in the detection of clinically insignificant cancers (9-12).

Another matter of debate is the contemporary strategy of extended prostate biopsy, which increases the number of needle cores from 8 to 13, which is a practice that could lead to a greater detection of clinically insignificant cancers. Conversely studies have shown that this practice is responsible for an increase of more than 30% in cancer detection not related to clinically insignificant cancer (13).

Histopathological findings and tumor characteristics have not been well characterized when the PSA cut-off is below 4 ng/mL in the extended prostate biopsy era. To our knowledge complete data including tumor volume have not been previously reported. The aim of this study was to compare the histopathological findings of extended prostate biopsy and radical prostatectomy in men with PSA levels lower or higher than 4 ng/mL.

MATERIALS AND METHODS

From January 1st 2005 to October 31st 2006, 1587 biopsies were examined in our laboratory. All information was available for 1081 patients. The mean age was 61.7 years, median 61 (range 31-93). The mean PSA was 7.43 ng/mL, median 5.5 ng/mL (range 0.3-146.0 ng/mL). The mean size of the prostate was 57.6 cm^3, median 48 cm^3 ranging from 15 to 275 cm^3, and the mean number of cores taken in each biopsy section was 15.5, median 14, ranging from 6 to 47.

Of the 1081 patients, 275 (25.4%) had PSA levels ≤ 4 ng/mL. The median age was 59 years (range 31-78), the mean size of the prostate was 40.6 cm^3 (SD 21.5) and the median number of cores taken in each biopsy section was 14, ranging from 6 to 27. The characteristics of the patients according the PSA levels are in Table-1.

The reason for the biopsy in the men with PSA under 4 ng/mL was available for only 71 (25.8%) patients. Abnormalities in the digital rectal examination was the primary cause, described in 33 (46.5%) patients, followed by suspicious or pre-malignant (prostate intraepithelial neoplasia (PIN) and atypical small acinar proliferation (ASAP)) lesion in previous biopsies in 27 (38.0%), persistent elevation of PSA in 5 (7.1%), family history of prostate cancer in 4 (5.6%) and cancer previously diagnosed in transurethral resection in 2 (2.8%).

Transrectal ultrasound guided prostate biopsies were routinely processed and examined by only one pathologist (KRL). Diagnosis was classified as: 1) benign; 2) suspicious but not conclusive for cancer, also known as ASAP; 3) PIN, and 4) cancer. When the diagnosis was adenocarcinoma, the Gleason score was used for histological differentiation and the tumor extension was shown by the number of cores positive for tumor and total percent of tumor in all cores seen.

A subset of 56 patients, from the 376 who were found to have cancer, underwent radical prostatectomy at our institution. The pathologic analyses of the prostatectomy specimens were completely sampled as described previously in detail (14). Organ-confined disease was defined as tumor that did not extend through the capsule, invade seminal vesicles, or metastasize to lymph nodes. Gleason score was used for grading. The tumor volume was determined as a percentage of the prostate gland involved by carcinoma, as estimated using the grid as described by Humphrey and Vollmer (15) and extrapolated to cm^3 for analysis. Staging followed the TNM 2002 recommendations (16).

The differences between the pathologic features were compared between patients whose cancers were detected at a PSA level between 0 and 4.0 ng/mL and those whose cancers were detected after the PSA level rose to greater than 4.0 ng/mL. Standard statistics, chi-square or Fisher's exact test, and Mann-Whitney test analysis were used to compare the data.

RESULTS

PSA was ≤ 4.0 ng/mL in 275 (25.4%) patients, with a mean of 2.85 ng/mL, (SD 0.94) and median of 3.04 ng/mL (range 0.3 to 4.0 ng/mL). The levels of PSA were between 0 to 1 ng/mL in 21 (7.6%),

Table 1 – *Characteristics of 1081 patients submitted to prostate biopsy between January 2005 and October 2006 considering the PSA level.*

	PSA		p Value
	> 4 ng/mL (n = 806)	**≤ 4 ng/mL** (n = 275)	
Age (years)	62.5 ± 8.7	59.3 ± 8.9	< 0.001
Number of cores	15 (6 – 47)	14 (6 – 27)	< 0.001
Prostate weight (g)	51.5 (16-275)	35.0 (15-120)	< 0.001

1.1 to 2 ng/mL in 34 (12.4%), 2.1 to 3 ng/mL in 82 (29.8%) and 3.1 to 4 ng/mL in 138 (50.2%) patients. The remaining 806 (74.6%) had a PSA higher than 4.0 ng/mL, with a mean of 8.99 ng/mL (SD 9.5 ng/mL), and a median of 6.6 ng/mL, ranging from 4.01 to 146.0 ng/mL.

Patients with PSA ≤ 4 ng/mL were significantly younger, with a mean age of 59.3 years (p < 0.001), and had lighter prostate glands 35.0g compared with 51.5g when PSA > 4 ng/mL (p < 0.001) (Table-1).

Considering the diagnosis, except for PIN, that was more frequently diagnosed in men with PSA ≤ 4 ng/mL, there was no statistical difference between the diagnosis of benign, ASAP and adenocarcinoma (p = 0.906) (Table-2).

Stratifying PSA levels for men with PSA ≤ 4.0 ng/mL, cancer was diagnosed in 1/21 (4.8%) patients with PSA level ≤ 1.0 ng/mL, 10/34 (29.4%) with PSA 1.1 to 2 ng/mL, 23/82 (28.0%) with PSA 2.1 to 3 ng/mL and 54/138 (39.1%) with PSA 3.1 to 4 ng/mL.

The cancer characteristics were similar for both groups (Table-3). The median Gleason score was 7 for both (p = 0.078), the median of number of cores positive for tumor was 4 and 3, respectively, for PSA > 4 ng/mL and PSA ≤ 4 ng/mL (p = 0.627). Considering the total percent of tumor involving all cores, patients with PSA > 4 ng/mL had a median of 11% versus 7% for patients with PSA ≤ 4 ng/mL (p = 0.042).

Considering the 71 patients who had information about the reason of the biopsy, we studied the characteristics of those 33 who were clinical staged T2 comparing with the 38 where digital rectal

Table 2 – *Diagnosis of prostate biopsy in 1081 patients with PSA ≤ 4 ng/mL and PSA > 4 ng/mL.*

	PSA		
Diagnosis	**> 4 ng/mL**	**≤ 4 ng/mL**	**Total**
Benign	357 (44.3%)	112 (40.7%)	469 (43.4%)
PIN	120 (14.9%)	64 (23.3%)	184 (17.0%)
ASAP	41 (5.1%)	11 (4.0%)	52 (4.8%)
Adenocarcinoma	288 (35.7%)	88 (32.0%)	376 (34.8%)
Total	806 (74.6%)	275 (25.4%)	1081 (100.0%)

ASAP = atypical small acinar proliferation; PIN = prostatic intraepithelial neoplasia.

Table 3 *– Tumor characteristics in prostate biopsies of 376 patients with PSA ≤ 4 ng/mL and PSA> 4 ng/mL.*

	PSA		p Value
	> 4 ng/mL (n = 288)	**≤ 4 ng/mL** (n = 88)	
Gleason score	7 (4 - 10)	7 (5 - 9)	0.078
Number of cores positive for tumor	4 (1 - 18)	3 (1 - 14)	0.627
Total percent of tumor	11 (0.1 - 100)	7 (0.1 - 90)	0.042

examination was normal. Among patients that had abnormalities in the digital rectal examination, cancer was diagnosed in 13 (39.4%), comparing with only 8 (21.1%) in 38 without abnormalities in the digital rectal examination ($p < 0.0001$). PSA levels were similar for both groups, 2.54 ng/mL for T2 patients and 2.73 ng/mL for T1, as was the Gleason score, mean 6.7 for the T2 and 6.1 for T1. Tumors were larger for T2 lesions, with mean number of cores positive for tumor 3.9 and mean total percentage 13.0%, versus 2.3 cores and 2.7% for T1 lesions.

Fifty-six patients underwent radical prostatectomy and the findings are shown in Table-4. Twelve had PSA ≤ 4 ng/mL. There was no statistical difference between Gleason score and tumor volume for both groups of patients. The median Gleason score was 7 for both groups ($p = 0.068$), and tumor volume was 10% or 3.1 cm^3 and 11% or 4.05 cm^3 for ≤ 4 ng/mL and PSA > 4 ng/mL, respectively ($p = 0.689$ for percentage and $p = 0.639$ for cm^3). There were no differences between the groups regarding extra-prostatic extension ($p = 0.424$), seminal vesicles infiltration ($p > 0.999$), lymph node metastasis ($p > 0.999$) and positive surgical margins ($p = 0.427$). One (8.3%) patient was stage pT3 with PSA ≤ 4 ng/mL and 10 were staged at this level (22.7%) with PSA > 4 ng/mL ($p = 0.424$).

In the group of patients with PSA ≤ 4 ng/mL there was no insignificant cancer as defined by Epstein et al. (17) as a tumor volume of less than 0.5 cm^3, Gleason score less than 7, and organ-confined. Additionally, one patient was stage pT3a, showing extra-prostatic extension and positive surgical margin.

COMMENTS

In order to minimize economic impact in the health system and maximize the effectiveness of detecting and treating CaP, various studies have aimed to find the best levels of PSA and its variations, especially PSA density and PSA kinetics (18). CaP screening programs have shown that using 4.0 ng/mL as a cutoff results in only clinically significant tumors being detected, and one third of the men treated for radical prostatectomy disease that had progressed beyond the prostate (8). Lowering PSA levels to 2.5 ng/mL seems to better detect organ-confined tumors, enhancing chances of disease-free and overall survival, particularly in younger men (19,20). In association with lowering PSA levels, the current practice of more intensive biopsy regimens could lead to the detection of non-significant tumors. It was the aim of our study to describe histopathological findings in extended prostate biopsy in patients with PSA levels lower than 4 ng/mL.

We have shown that cancer was diagnosed in 32% of patients, which is the same proportion of patients diagnosed with cancer with a PSA > 4 ng/mL, which is the traditional cutoff for prostate biopsy. We also observed that cancer was diagnosed even in patients with a very low level of PSA, below 1 ng/mL, and there was significantly worse disease as PSA levels rose. Malignancy was observed in 29.4%, 28.0% and 39.1% of patients with PSA levels from 1.1 to 2 ng/mL, 2.1 to 3 ng/mL, and 3.1 to 4 ng/mL, respectively. Our numbers were even higher than those reported by the Prostate Cancer Prevention Trial, which

***Table 4** – Patient age and tumor characteristics in radical prostatectomy specimens when PSA was ≤ 4 ng/mL or > 4 ng/mL.*

	PSA		p Value
	> 4 ng/mL (n = 44)	**≤ 4 ng/mL** (n = 12)	
Age (years) mean ± SD	61.2 ± 7.8	61.5 ± 8.5	0.910
Gleason score Median (min - max)	7 (5 - 9)	7 (6 - 8)	0.068
Tumor volume (cm^3) Median (min - max)	4.05 (0.5 - 29.0)	3.10 (0.5 - 10.0)	0.639
%Gleason 4 Median (min - max)	34.3 (0 - 100)	24.0 (0 - 100)	0.079
Extra prostatic (+)	10 (22.7%)	1 (8.3%)	0.424
Seminal vesicles (+)	2 (4.5%)	-	> 0.999
Lymph node metastasis	2 (4.5%)	-	> 0.999
Margin (+)	11 (25.0%)	1 (9.3%)	0.427
Stage			0.424
pT3	10 (22.7%)	1 (8.3%)	
pT2	34 (77.3%)	11 (91.7%)	

indicated that the overall cancer detection was 15.2%. They found cancer in 6.6% of patients when PSA was less than 0.5 ng/mL, 10.1% when it was between 0.6 to 1.0 ng/mL, 17.0% from 1.1 to 2 ng/mL, 23.9%, from 2.1 to 3.0 ng/mL, and 26.9% when PSA was 3.1 to 4 ng/mL (21). The median PSA value for men in their 40s and 50s is approximately 0.7 ng/mL and 0.9 ng/mL, respectively, and a baseline PSA level greater than the median for each age group was related to a 12 to 22-fold greater risk of having CaP (22). Although the American Cancer Society Guidelines recommend screening for CaP before age 50 only in men with risk factors for CaP, including African-American descent or a strong family history of CaP, authors have recommended the measurement of baseline PSA at age 40, which could allow the determination of PSA kinetics, and is a sensitive marker for prostate cancer diagnosis and prognostic prediction (22). This knowledge may be changing the standard practice of urology since in this present study patients with PSA ≤ 4 ng/mL were significantly younger. Bill-Axelson et al. (23) have claimed that initiating screening before age 50 and detecting cancer earlier should prevent death, especially because patients undergoing radical prostatectomy younger than 65 years-old have reduced CaP-specific mortality. Sun et al. (18) have previously shown that in patients younger than 50, PSA levels of 2.5 ng/mL have specificity of 94% for detecting cancer, and strongly recommend measuring PSA in younger men. Together with the number of patients we have just found, biopsy should be recommended when PSA is higher than the median for that specific age, since almost one third of men will be diagnosed CaP.

Gleason score is the most important isolated prognostic factor, and we observed no difference in the Gleason score between the groups with PSA lower or higher than 4 ng/mL, which both had a median Gleason score of 7. Furthermore, tumor volume in prostate biopsy has been addressed as a very important predictor of cancer extension and outcome. Multiple measurements have been used, including number of positive cores, total millimeters of cancer amongst all cores, percentage of each core occupied by cancer and total percent of cancer in the entire specimen. The best method for determining tumor burden is not yet clear, but estimating a percentage is easy and has been demonstrated to be a useful predictor of tumor extension and cancer-free survival rate (24,25). In the current study we showed no difference considering the number of cores compromised by tumor, but tumors were smaller when PSA ≤ 4 ng/mL, with a total percentage of 7% against 11% when PSA > 4 ng/mL. Smaller tumors are also more likely to be organ-confined. This was not confirmed for patients undergoing radical prostatectomy where tumor characteristics, including volume were very similar to those with PSA higher than 4 ng/mL. One explanation for this fact is a bias considering the choice of treatment. Urologists could have preferred surgery for those patients with other associated adverse characteristics leading to similar results, mostly taking into account tumor volume. This data needs to be clarified in further series.

The detection of organ-confined cancer when PSA is lower than 4 ng/mL could cause some apprehension in treating "harmless" or insignificant cancer. Insignificant cancer is defined as tumor with Gleason pattern less than 4 or 5, organ-confined and volume less than 0.5 cm^3 (17). Reports of fewer than 10% of insignificant cancers have been published, and our series is in agreement with the literature since we did not find any clinically insignificant cancer. In addition to the low number of patients who underwent radical prostatectomy with PSA ≤ 4 ng/mL, our data show tumors that can not be considered insignificant, with mean Gleason score 6.6, median 7, ranging from 6 to 8. In addition it is known that presence of tertiary Gleason 4 or 5, and the percent of a higher Gleason pattern impact the prognosis of prostate cancer. The mean percent of Gleason pattern 4 for this group of patients was 32%, which means a 30% reduction in disease free survival in 10 years (26). Considering tumor volume, McNeal (27) had found good prognosis for tumors with volume less than 4 cm^3. The mean tumor volume of our surgical specimens was 3.9 cm^3, but 33% were higher than 5 cm^3, with one 10 cm^3, which could be considered a huge tumor, with a 33% probability of recurrence in 10 years (26).

One limitation of our study was the lack of data of PSA velocity (PSAV). PSAV measurement has been shown to be very helpful, as clinically significant prostate cancer is more likely to be found in men with a rapidly rising PSA. Studies suggest that for men with a total PSA higher than 4 ng/mL, a PSA velocity of 0.75 ng/mL/year is an indication for biopsy. However, in men whose total PSA level is lower than 4 ng/mL, an ideal cutoff has not yet been determined and should range from 0.1 to 0.5 ng/mL/year (28-30). It has been demonstrated that for each 0.1 ng/mL per year increase in PSA, the likelihood of death from prostate cancer increases 15%. For men with a consistent increase in PSA of 0.35 ng/mL per year or higher, the relative risk of dying of prostate cancer is 5 times higher in the next 2 to 3 decades than for men with lower PSA increases(31). Nevertheless, this weak point may be overcome by the findings recently published by Yu X et al. (32). These authors have shown a correlation between total PSA and PSAV, describing a PSAV of more than 2 ng/mL per year in only 1% and 14% of patients whose PSA total levels were lower than 2.5 ng/mL or between 2.5 ng/mL and 4 ng/mL, respectively, indicating a less aggressive and more curable disease.

In conclusion, our findings show that in the extended biopsy era cancer will be detected in 32% of patients when biopsy is performed with PSA below 4 ng/mL. Gleason score and number of cores positive for cancer are similar to those with PSA > 4 ng/mL. Although cancer characteristics in radical prostatectomy were comparable for both groups as Gleason score, percentage of Gleason pattern 4, tumor volume and staging, patients that undergo biopsy with PSA lower than 4 ng/mL are younger and have smaller tumors in biopsies as measured by the total percent of tumor, and, consequently have better chances of having less aggressive tumors. Because of the small number of patients submitted to radical prostatectomy with PSA ≤ 4 ng/mL, other studies, with larger series are warranted to confirm our findings.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

This is a well conducted study concluding that when PSA is below 4 ng/mL, cancer is detected in a proportion equal to the proportion diagnosed with a PSA > 4 ng/mL, and tumor characteristics are similar between the two groups. These findings are supported by other studies. Krumholtz et al. (1) evaluated the pathologic characteristics of clinical stage T1c prostate cancers detected in the 2.6 to 4.0 ng/mL PSA range and compared them with cancers concurrently detected in the 4.1 to 10.0 ng/mL. The authors found that men detected at the 2.6 to 4.0 ng/mL PSA range had significantly smaller cancer volumes however, no difference was found in the proportion of tumors that met previously published criteria of "clinically insignificant" (organ confined, less than 0.2 cm^3 tumor volume, and Gleason sum 6 or less) or "clinically unimportant" (organ confined, less than 0.5 cm^3 tumor volume, and Gleason sum 6 or less) tumors. Using the lower PSA cutoff point resulted in the detection of a significantly higher percentage of organ-confined tumors. The authors conclude that the use of a 2.6

ng/mL PSA threshold for screening resulted in the more frequent detection of small, organ-confined tumors without over detecting possibly clinically insignificant ones. Obviously, additional studies in larger populations with longer follow-up are needed to confirm these findings.

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EDITORIAL COMMENT

Early in the PSA era patients with a serum prostate-specific antigen (PSA) level > 4.0 ng/mL and a normal digital rectal examination (DRE) were recommended to undergo prostate biopsy because of a 20-30% risk of prostate cancer at a pre-specified sensitivity of 95%. The majority of such patients have clinically important cancers and the rate of indolent disease, defined as specimen Gleason score 2-6, no extra-prostatic extension, and no Gleason pattern 4/5 is generally < 20%. Many have argued that a PSA threshold for biopsy of 4.0 is more frequently associated with under- rather than over-diagnosis as rates of non-organ-confined cancer (25-35%) are 2 to 4 times higher than indolent cancers, whereas cancers detected in the 2.6-4.0 PSA range are more likely to be organ-confined without substantial differences in the rate of low-grade or indolent cancer. In a longitudinal screening study, a decreased risk of PSA-defined biochemical recurrence was observed for patients treated by radical prostatectomy after lowering the PSA threshold for biopsy from 4.0 to 2.5 (1). As such, a lowering of the PSA level for biopsy to 2.5 has been advocated to increase the detection of clinically significant cancers at a more curable stage, and this had been adopted in the guidelines of some professional societies (2).

The Prostate Cancer Prevention Trial (PCPT) has challenged the validity of any PSA threshold for biopsy as no specific PSA value had sufficient sensitivity and specificity for the detection of prostate cancer to be clinically useful (3). Based on the results of patients who had an end-of-study biopsy without usual clinical implications, there was a continuum of cancer risk at all PSA values. Among patients with a PSA < 1.0, 1.1-2.0, and 2.1-3.0, the cancer detection rate was 9%, 17%, and 24%, respectively and the corresponding proportion of cancers graded as Gleason 7-10 was 11%, 12% and 19% (4). These results indicate that there is no PSA below which the risk of having cancer is zero.

In the current study, Leite et al. report on the biopsy and pathological characteristics of a cohort of patients biopsied with a PSA < 4. Reasons for biopsy included abnormal DRE, prior biopsies showing atypical small acinar proliferation or prostatic intraepithelial neoplasia, persistently elevated PSA and negative prior biopsy, or a positive family history, so that the population studied is not fully representative of the general population usually subjected to opportunistic screening. Nonetheless the findings are illuminating, demonstrating similar rates of prostate cancer in those with a PSA < 4 vs. > 4 (32 vs. 36%), no difference

in tumor grade (median score 7 in both groups), and slightly fewer positive cores in the PSA < 4 group. In the small subset of patients who underwent radical prostatectomy, there was no difference in tumor volume, grade, or pathological stage. Surprisingly, and unlike our own experience with similar patients where the incidence of indolent cancers is higher in men with PSA < 4, the authors found no indolent cancers as defined by Epstein's criteria of organ-confined tumors of volume < 0.5 cc and grade < 7. This likely reflects the indications for biopsy in this population and less widespread and repeated screening than in the United States.

What then is the optimal PSA cutoff for recommending biopsy in 2008? The theoretical answer is that the optimal threshold is one that maximizes detection of biologically significant but curable cancers, reduces prostate-cancer-specific mortality, and minimizes over-diagnosis of indolent disease. The practical answer is one that recognizes that PSA represents a continuum of risk that is also impacted by many other factors, and that the best way decides whom to biopsy includes a consideration of all of the relevant factors. At the Cleveland Clinic, we have stopped reporting a "normal" cutoff for PSA on our lab reports and substituted the following: "Published data from the Prostate Cancer Prevention Trial demonstrated that there is no PSA level below which the risk of having prostate cancer is zero. For an individual patient, the significance of a PSA level should be interpreted in a broad clinical context, including age, race, family history, digital rectal exam, prostate size, results of prior prostate biopsy, and use of 5 alpha reductase inhibitors. Considering the high incidence of asymptomatic cancer in the general population that may not pose an ultimate risk to the patient, the decision to recommend urological evaluation or prostate biopsy should be individualized after considering all of these factors." We have encouraged the use of the PCPT risk calculator (available at www.compass.fhcrc.org/edrnnci/bin/calculator/main.asp) as one tool (validated published nomograms for this purpose also exist) to achieve the goal of defining individual risk prior to recommending biopsy. Using this calculator, a 55 year old Caucasian male with a negative DRE, a PSA of 1.5, and no family history of prostate cancer has a 19% risk of having prostate cancer but only a 2% risk of having high grade (Gleason 7 or greater) disease, information that can give the patient a more precise estimate of the risks and benefits of undergoing biopsy before deciding whether to have it done. For a 55 year old African American man with a normal DRE, a positive family history, and PSA of 2.4, the calculator estimates a risk of any cancer at 31% and of high grade cancer at 8%; here the risk: benefit ratio probably justifies biopsy even though his PSA is generally considered below the current threshold. Adoption of this approach outside of the U.S. requires construction and validation of similar models on local populations; ultimately, proof of the utility of PSA screening at all awaits the reporting of large screening trials (the ERSPC and PLCO) currently nearing completion.

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Updated Results of High-Dose Rate Brachytherapy and External Beam Radiotherapy for Locally and Locally Advanced Prostate Cancer Using the RTOG-ASTRO Phoenix Definition

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ABSTRACT

Purpose: To evaluate the prognostic factors for patients with local or locally advanced prostate cancer treated with external beam radiotherapy (RT) and high dose rate brachytherapy (HDR) according to the RTOG-ASTRO Phoenix Consensus Conference.

Materials and Methods: The charts of 209 patients treated between 1997 and 2005 with localized RT and HDR as a boost at the Department of Radiation Oncology, AC Camargo Hospital, Sao Paulo, Brazil were reviewed. Clinical and treatment parameters i.e.: patient's age, Gleason score, clinical stage, initial PSA (iPSA), risk group (RG) for biochemical failure, doses of RT and HDR were evaluated. Median age and median follow-up time were 68 and 5.3 years, respectively. Median RT and HDR doses were 45 Gy and 20 Gy.

Results: Disease specific survival (DSS) at 3.3 year was 94.2%. Regarding RG, for the LR (low risk), IR (intermediate risk) and HR (high risk), the DSS rates at 3.3 years were 91.5%, 90.2% and 88.5%, respectively. On univariate analysis prognostic factors related to DSS were RG ($p = 0.040$), Gleason score ≤ 6 ng/mL ($p = 0.002$), total dose of HDR ≥ 20 Gy ($p < 0.001$) On multivariate analysis the only statistical significant predictive factor for biochemical control (bNED) was the RG, $p < 0.001$ (CI - 1.147-3.561).

Conclusions: Although the radiation dose administered to the prostate is an important factor related to bNED, this could not be established with statistical significance in this group of patients. To date , in our own experience, HDR associated to RT could be considered a successful approach in the treatment of prostate cancer.

Key words: *prostate cancer; radiotherapy; brachytherapy; recurrence; treatment failure*

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INTRODUCTION

Prostate cancer (PCa) is one of the most prevalent malignancies affecting men in the developed world. For male population of western countries, the probability of deaths from PCa is about 3% (1). In Brazil for 2006, 47,280 new cases of PCa were expected to be diagnosed (2). The optimal management of both localized and locally advanced PCa remains controversial with a consensus that surgery, radiotherapy, hormonal therapy, and watchful waiting can be used isolated or in combination to treat the different risk groups (RG) for biochemical failure (BF) (3).

Radiotherapy (RT) has been used for years to treat patients with poor clinical conditions or with advanced stages of the disease, but in the past two decades it has emerged as an option to surgery in some specific cases. For patients treated with RT

significant clinical data are available demonstrating that patients have a significantly better outcome as the dose administered to the prostate is increased (4-6). There are also a number of published results demonstrating that conformal high dose rate (HDR) brachytherapy is a successful method for delivering higher dose of radiation to the prostate sparing the normal surrounding tissues (7,8). Indeed, HDR is a very precise and conformal way of dose delivery with cell killing effects comparable to three-dimensional conformal (3DRT) and intensity modulated (IMRT) external beam RT (9). HDR also has some potential additional advantages over normal tissue sparing and on reducing miss dose to the prostate, due imprecise target localization, treatment setup uncertainties, organ motion and or deformation during the treatments, with a relative low incidence of severe acute and late side-effects (10-12).

MATERIAL AND METHODS

This study on human beings has been approved by the local Ethics Committee of Hospital AC Camargo, Sao Paulo, Brazil. The charts of patients with initial or locally advanced biopsy proven prostate adenocarcinoma, treated with pelvic localized conventional or 3DRT in combination with HDR at the Department of Radiation Oncology, Hospital AC Camargo, Sao Paulo, Brazil were retrospectively reviewed. Details such as Gleason score (GS), the initial PSA value (iPSA) and clinical stage (CS) using the 1992 AJCC clinical stage were collected from the hospital records to define the risk group for biochemical failure, according to the following classification: low risk subgroup (LR) encompassed patients with CS T2a or lesser, GS less than 7 and initial PSA value equal or lesser than 10 ng/mL. Patients with either stage T2b, GS 7 or initial PSA value ranging from 10-20 ng/mL were considered intermediate risk (IR) and the remaining patients or patients who presented two or more of the characteristics of the IR subgroup were grouped into the high risk (HR) group for BF (13). At the discretion of the referral urologists, patients in all groups received a course of neoadjuvant central or peripheral androgen blockage (NAAD), with goserelin and or flutamide or ciproteron acetate, 3 to 6 months prior to RT.

In the first three years of treatment, conventional (2D) RT planning was used for all patients, based on diagnostic computed tomography scan (CT), urethrogram and rectal contrast agent to assist in defining prostate, seminal vesicles and normal tissue volumes at risk. The prostate and seminal vesicles were irradiated t via a 6 MV Varian linear accelerator, with four-field box technique and individual protections with cerrobend blocks. After 1999, all patients were treated with localized three-dimensional conformal (3D) RT.

The technique of HDR has been previously reported in the literature (9). In brief, the implant procedures were performed 10 to 15 days after the end of RT, under spinal anesthesia with the patient in lithotomic position. Two metallic markers were inserted into the gland, one in the apex and the other at the base of the prostate, to ascertain quality control of any needle displacement during the treatment and to allow corrections whenever it was necessary. All the implants were performed with steel needles inserted through a perineal template, which was sutured to the perineum. The needles were uniformly placed into the entire prostatic volume, but avoiding the urethra. In the initial years, orthogonal X-rays were used for planning and dosimetric calculations. On August 2000, we switched to 3D image guided CT based planning using the BrachyVision® Planning System (Varian Medical Systems, Inc., Palo Alto CA., USA)

After completion of treatment, patients were seen in follow-up 1 month later and subsequently every 2-4 months for the first 24 months. Thereafter patients were seen at follow-up every 6-12 months.

The endpoint was to evaluate the biological non evidence of disease (bNED), calculated as the interval from pathologic diagnosis of PCa to BF. Date of BF, a rise in 2 ng/mL after the nadir had been reached, was defined according to the RTOG-ASTRO Phoenix Consensus Conference (14). Pearson chi-square and Student's-t tests were used to compare differences in categorical and continuous patient characteristics, respectively. Survival data were generated using the Kaplan-Meier method, with log-rank test used to compare equality of survivor functions. The Cox proportional hazard model was used for multivariate

analysis, using a stepwise procedure. Statistical tests were performed using SPSS 13.0 (SPSS, Chicago, IL).

RESULTS

A total of 234 patients were treated with combination of RT and HDR between 1997 and 2005 at the Department of Radiation Oncology, Hospital AC Camargo, Sao Paulo, Brazil. Fifteen patients were excluded from the study because they were lost to follow-up after treatment. Seven patients had whole pelvis RT and were also excluded from the analysis. Three patients did not reach a nadir value below 10 ng/mL after the end of treatment and a review of their charts showed that they already had metastatic disease at the time of treatment, and therefore also excluded from the study. Median age of the remaining 209 patients was 68 years (range, 47-83 years). Median follow-up was 5.3 years (range, 2-10). There were 77 (36.8%) of patients in the LR, 65 (31.1%) in the IR group and 67 (32.1%) in the HR group. The patients were well balanced into all groups, with no statistical significant difference in between the different RG for BF (p = 0.437). Characteristics of patients are shown in Table-1.

The dose of RT ranged from 36 to 54 Gy (median 45 Gy) given in 20 to 30 daily fractions of 1.8 or 2.0 Gy. The total RT treatment time ranged from 4 to 7 weeks (median 5 weeks). The HDR was performed after one to two weeks of the completion of RT in 204 patients. Five patients started their treatment by HDR and after that had a course of RT. The total treatment time ranged from 5 to 9 weeks (median 7 weeks). The dose of HDR ranged from 16 to 24 Gy given in 4 fractions, BID in two days. Median HDR dose was 20 Gy.

A hundred and eight (51.7%) patients had no NAAD. Of the patients who had NAAD, 70 (33.5%) had central and 31 (14.8%) patients had peripheral blockage alone.

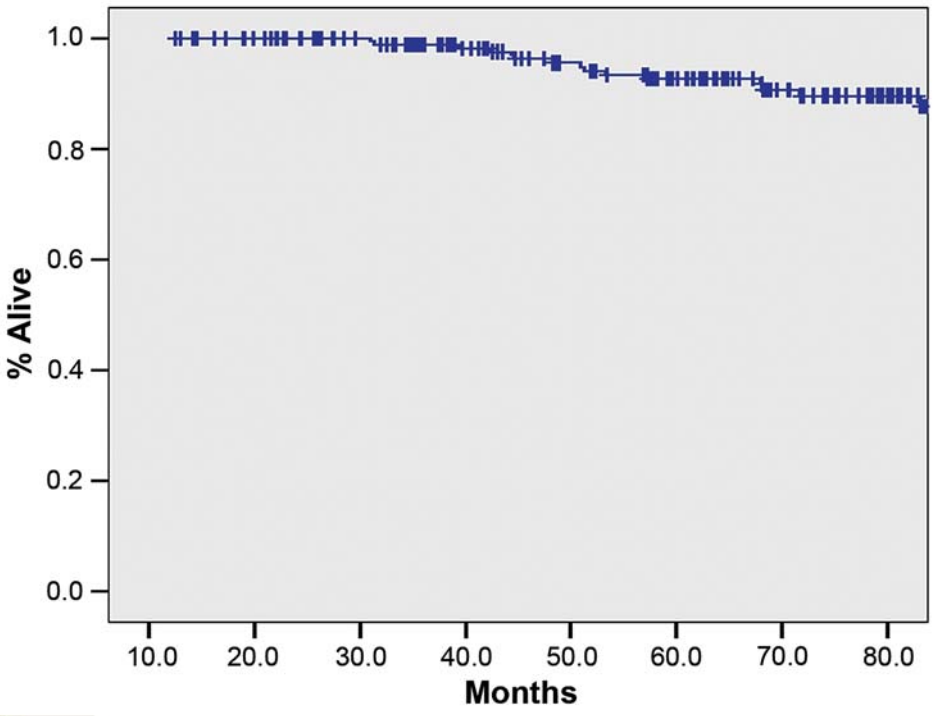
Overall survival (OS) rate at 3.3 years was 97.8%. The 5- and 10-year actuarial OS rates were 95.7% and 90.6%, respectively (Figure-1). Eleven patients had died at the time of this analysis. Five (2.4%) patients died due prostate cancer disease progression and 6 (2.9%) of other causes (3 of cardiologic related disease, 2 of a new second primary tumor and 1 of surgical complication after a salvage prostatectomy). For the LR, IR and HR, the bNED rates at 3.3 years were 91.5%, 90.2% and 88.5%, respectively. Actuarial bNED rates at 5- and 10-year were 95.7% and 59.6%, as shown in Figure-2.

On univariate analysis the prognostic factors related to better bNED rates were RG (p = 0.040), GS ≤ 6 ng/mL (p = 0.002), total dose of HDR ≥ 20 Gy (p < 0.001), use of three dimensional planning for HDR

Table 1 *– Patients characteristics.*

Variables	N	%	Range	Median
Age (years)			47-83	68.0
iPSA (ng/mL)			4-175	10.5
Follow-up (months)			24-120	62.9
Ethnicity				
Asiatic	8	3.8		
Caucasian	180	86.2		
African	14	6.7		
Unknown	7	3.3		
Clinical stage				
T1	95	45.5		
T2a	72	34.4		
T2b	19	9.1		
T3a	23	11.0		
Gleason score				
≤ 6	148	70.8		
7	41	19.6		
≥ 8	20	9.6		
RG				
Low	77	36.8		
Intermediate	65	31.2		
High	67	32.2		
NAAD				
No	108	51.7		
Yes	101	48.3		
Total	209	100.0		

iPSA = initial PSA value; NAAD = neoadjuvant androgen deprivation; RG = risk group for biochemical failure.



At Risk	209	181	154	149	133	117	85	59
(%)		100	86.6	73.6	71.3	63.6	56.0	40.7	28.2

Figure 1 – *Overall survival.*

($p < 0.001$) Table-2. We also explored the influence of NAAD according to RG, observing no statically significant benefit of association of NAAD in any group ($p = 0.061$).

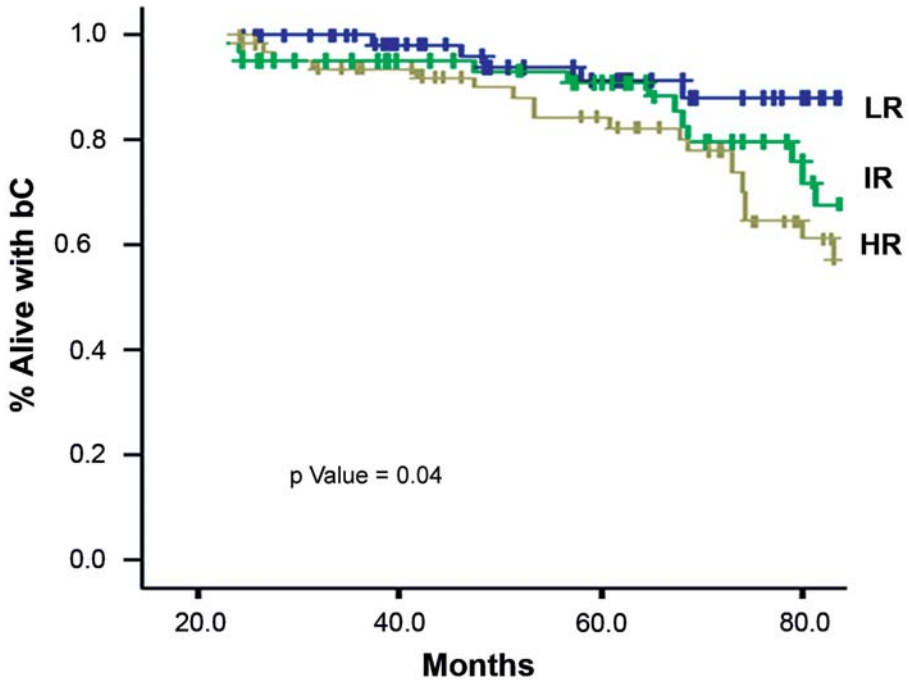
On multivariate analysis, the only statistical significant predictive factor related to a better bNED rate was the RG, $p < 0.001$ (CI - 1.147-3.561). The hazard ratio was 1.7 and 2.4 times less chance of achieving a bNED for IR and HR when compared to LR, respectively, (Figure-3).

COMMENTS

Several retrospective studies with more than 5-year follow up have previously described the outcome of patients treated with combination of RT and HDR (8,14,15), but data from prospective randomized trail comparing results of this combination with dose escalation RT3D or IMRT is still missing.

The main advantage of HDR is its ability to deliver a relative high dose of radiation within a well-defined volume, with a rapid fall-off of dose outside the implanted area. This approach is ideal for the treatment of prostate cancer, where the gland lays very close to critical normal tissues, in particular the anterior rectal wall and bladder neck (9).

Galalae et al. (16) also investigated the long-term outcome by RG using HDR and RT with or without NAAD. There were 611 patients grouped as follows: 46 patients into LR, 188 patients into IR and 359 patients considered HR. Using the ASTRO definition for BF these authors observed that the actuarial bNED and disease free survival rates at



Low risk (LR)	75	52	36	20
Intermediate risk (IR)	66	49	38	20
High risk (HR)	68	55	42	19

Figure 2 – *Biochemical control according to the risk group for biochemical failure.*

5-year and 10-year were 77%, 67%, 73% and 49%, respectively. For the different RG the actuarial 5-year bNED rates were 96% for LR, 88% for IR and 69% for HR. They observed that GS and RG were statistical significant predictive factors of bNED, which were also confirmed in the present study, and GS ($p = 0.002$) and group risk ($p = 0.050$) were statistical significant predictive factors for BF. They also observed that CS and iPSA were also statistical significant predictive factors, which was not confirmed in this study.

Deger et al. (17) evaluated 422 patients with localized prostate cancer treated between 1992 and 2001 with HDR and 3DRT. All patients underwent laparoscopic pelvic lymph node dissection to exclude patients with lymphatic involvement. The BF was also defined according to the ASTRO criteria. The bNED according to RG were 100% T1, 75% for T2 and 60% T3 at 5 years. Five-year bNED were 81% in the LR, 65% in the IR and 59% in the HR. Five-year OS and bNED were 87% and 94%, respectively. They also observed that iPSA, RG and age were significantly related to bNED. In our study the use of NAAD was not associated with better bNED ($p = 0.425$). When the subgroups according to risk for BF were analyzed, there was not a statistical significance for a better bNED related to the use or not of NAAD ($p = 0.875$).

There are a scarce number of papers that have published the results of HDR and RT for PCa using the RTOG-ASTRO Phoenix definition. This definition states that "To avoid the artifacts resulting from short follow-up, the reported date of control should be

Table 2 – *Univariate analysis.*

Variables	Total	bNED	%	p Value*
Age				
< 60	25	20	80.0	0.777
61-70	88	70	79.5	
> 70	96	83	86.5	
iPSA				
≤ 10	106	92	86.8	0.788
10-20	61	49	80.3	
> 20	42	32	76.2	
RG				
LR	77	72	93.5	0.040
IR	65	53	81.5	
HR	67	48	71.6	
Gleason score				
≤ 6	148	128	86.5	0.002
7	41	32	78.0	
≥ 8	20	13	65.0	
NAAD				
Yes	106	90	84.9	
No	103	83	80.6	0.425
HDR-BT (Gy)				
< 20	114	91	79.8	< 0.001
≥ 20	95	82	86.3	
EBRT (Gy)				
< 50	133	110	82.7	0.324
≥ 50	76	63	82.9	
3DHDR				
No	147	120	81.6	< 0.001
Yes	62	53	85.5	

bNED = biochemical control; iPSA = initial PSA value; RG = risk group for biochemical failure; LR = low risk; IR= intermediate risk; HR = high risk; NAAD = neoadjuvant androgen deprivation; HDR-BT = high dose rate brachytherapy; EBRT = external beam radiotherapy; BED = biological effective dose; 3DHDR = high dose rate brachytherapy based on three dimensional planning. p = test equality of survival distribution, 95% confidence interval.*

listed as 2 years short of the median follow-up" (14). Chin et al. (18) related the results of 65 consecutive patients treated between 1998 and 2004 with combination of RT and HDR given in 2 fractions. Sixty patients (92.3%) were considered IR or HR. With a median follow-up of 3.5 years (range 0.6-5.8), two patients had died of metastatic disease and other four patients had BF, giving a 3-year actuarial bNED rate of 90.8%. Yamada et al. (19) also reported the results of 105 patients consecutively treated between 1998 and 2004 with RT (45-50.4 Gy) and HDR (5.5-7.0 Gy per fraction). With a median follow-up of 44 months (8-79 months), the actuarial 5-year bNED rates for LR, IR and HR were 100%, 98%, and 92%, respectively. In the current study the actuarial bNED rates at 5-year were 91.8% for LR group, 79.3% for IR group and 69.1% for HR group (p = 0.040), respectively.

Patients considered HR have more chances of BF. This phenomenon could be a consequence of current inadequate imaging of lymph node or bone metastasis or due subclinical metastatic spread that remains undetectable during radical treatment. However, tumor biology itself could lead to the progression of the disease in the HR group. As a consequence, risk-adapted therapy is very important in these cases. The combination of RT and HDR is an alternative strategy of dose escalation that can potentially achieve a better bNED, but for patients at HR the localized dose delivered by HDR may be a potential disadvantage, because a microscopic spread outside the prostate and even its capsule may occur. In these cases, the combination of HDR and RT can provide treatment to potential areas of microscopic spread. What is still not answered is if adding pelvic radiation, instead to localized RT in combination to HDR for PCa patients with a more than 15% risk of positive lymph nodes will really improve outcome.

The use of NAAD still remains controversial for patients with IR to HR. Martinez et al. (20) in a study of 1,260 patients treated with pelvic RT and HDR observed similar OS, DFS and bNED for patients who were treated with or without the addition of a course of NAAD up to 6 months prior to radiation. They observed that NAAD did not confer a therapeutic advantage, but rather added side effects and cost. Furthermore, for the most unfavorable group, there was a higher rate of distant metastasis and more prostate cancer-related deaths. We did not observe a statistical significant benefit on bNED rates with the use of NAAD in none of the RG.

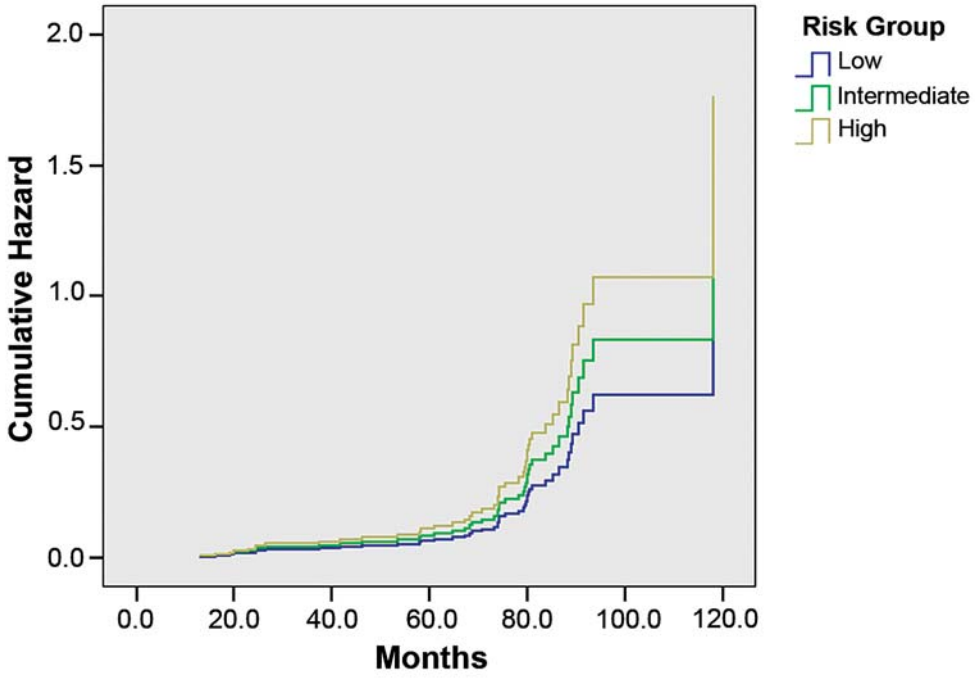


Figure 3 *– Hazard functions according to the risk group for biochemical failure.*

Aström et al. (21) published their results in terms of bNED for 214 patients consecutively treated from 1988 to 2000. With a median age of 64 years (50-77) and median follow-up of 4 years (12-165 months), they reported that NAAD was given to 150 patients (70%). The overall 5-year bNED was 82%, and for the LR, IR and HR was 92%, 88% and 61%, respectively.

The use of NAAD and androgen blockage during RT was published by Hsu et al. (22). They reported on their initial 64 patients treated with HDR - 18 Gy given in 3 fractions - to boost RT (45 Gy in 5 weeks). The median follow-up was 50 months (range 25-68 months) and the 4-year actuarial OS and DSS were 98% and 92%, respectively.

The use of HDR to boost RT is observed worldwide . A Spanish experience using HDR combined with RT was reported by Prada Gomes et al. (23). Between 1998 and 2004, 100 patients considered IR or HR were treated with 46 Gy of RT to the pelvis and 2 HDR brachytherapy fractions (each of 1150 cGy) at the end of weeks 1 and 3 of a 5-week RT course. With a median age of 67 years (range 49-78) and median follow-up of 28 months (range: 12-79), the 5-year OS and DSS were 99% and 87% respectively.

From Japan, Shigehara et al. (24) evaluated the efficacy of HDR combined with RT. Ninety-seven patients were treated between 1999 and 2003, and 84 patients were analyzed. HDR total dose was 18 Gy given in 3 fractions complemented by RT at a dose of 44 Gy. The 4-year OS and bNED rates were 87.2% and 82.6%, respectively. Prostate-specific antigen progression-free survival rates of groups with GS< 7 and GS > or = 7 were 92.8% and 60.1%, respectively. Oh et al. (25) reported results of 35 HR patients treated between 1995 and 2002. The use of NAAD lasted for a median period of 7 months, followed by concomitant and adjuvant androgen blockage (median time 40 months). The 5-year actuarial bNED rate was 62%. No patients experienced local and/or regional relapse with no distant progression. The 5-year actuarial DSS and OS rates were 89% and 87%, respectively.

Preliminary results of an ongoing randomized phase 3 trial with 65 consecutive patients treated with HDR and RT between 1998 and 2004 were published by Chin et al. (26). The median patient age of 67.3 years with the majority of them IR or HR (92.3%). With a median follow-up of 3.5 years (range 0.6-5.8), they observed that 2 (3%) patients had died of metastatic disease and another 4 (6%) patients had PSA relapse, giving a 3-year actuarial bNED of 90.8%.

Vargas et al. (27) performed a matched-pair analysis of patients treated with combined RT and HDR from January 1993 to March 2003. A total of 1,432 were evaluated. There were 755 cases identified as having a risk of positive pelvic lymph nodes of more than 15% using the Roach formula. Of these, 255 cases were treated without pelvic RT and randomly matched by GS, CS and iPSA to 500 cases treated with pelvic RT, resulting in 250 pairs. Based on these results they observed that BF, and OS were not significantly different for patients treated with pelvic radiotherapy. At a median follow-up of 4 years the bNED and OS rates were 78%, 86%, 89% and 88%, respectively. In our analysis, the actuarial 5- and 10-year OS were 95.7% and 90.6%, while the actuarial bNED rates at 5- and 10-year for the different RG were 91.8% and 82.3% for LR, 79.3% and 67.7% for IR, and 68.5% and 41.3% for HR ($p = 0.040$), respectively.

Our results and others have suggested that bNED is related not only clinical characteristics of patients, as RG and GS, but it is also related to treatment parameters as the total dose given to the prostate, although this could not be proved with statistical significance in this group of patients. In conclusion, we observed that the bNED rates at 3.3 years, reported as 2 years short of the median follow-up, were 91.5%, 90.2% and 88.5% for the LR, IR and HR, respectively. To date, in our own experience, HDR associated to RT could be considered a successful approach in the treatment of prostate cancer.

CONFLICT OF INTEREST

None declared.

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Inverse Correlation between Testosterone and Ventricle Ejection Fraction, Hemodynamics and Exercise Capacity in Heart Failure Patients with Erectile Dysfunction

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ABSTRACT

Background: Neurohormonal activation and abnormalities in growth hormone and testosterone concentrations have been reported in heart failure (HF). Erectile dysfunction(ED) is common in these patients and contributes to a low quality of life. No data are known regarding the correlation between testosterone and hemodynamics, exercise capacity and cardiac function in HF patients with ED, a marker of endothelial dysfunction. The aim of this study was to correlate testosterone levels with cardiac function, hemodynamic and exercise capacity in HF patients with ED.

Materials and Methods: Fifteen HF patients underwent a six-minute treadmill cardiopulmonary walking test (6'CWT) and, ten minutes later, a maximum cardiopulmonary exercise test. Also, testosterone and other hormones were determined at rest.

Results: Among hemodynamic variables only diastolic blood pressure on 6'CWT was correlated with testosterone levels($r = -0.66$, $p = 0.007$). The variables on exercise tests, VE/VCO_2 slope and oxygen consumption did not show any correlation, except the distance at 6'CWT ($r = 0.50$, $p = 0,047$). Right and left ventricle ejection fraction showed inverse correlation with testosterone ($r = -0.55$, $p = 0.03$ and $r = -0.69$, $p = 0.004$ respectively).

Conclusion: Testosterone levels correlated directly with distance at six-minute cardiopulmonary walk test and inversely with diastolic blood pressure, right and left ventricle ejection fraction in heart failure patients with erectile dysfunction. Further elucidation of mechanisms as regards testosterone action in these patients is warranted.

Key words: *heart failure; hemodynamics; physical activity; testosterone; erectile dysfunction*
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INTRODUCTION

Heart failure (HF) can be considered as the last stage of heart disease and a significant cause of mortality and morbidity worldwide (1). The left ventricular systolic dysfunction and limited exercise capacity manifested by breathlessness and fatigue are determinants of mortality and clinical events in the follow-up of HF patients. (2,3). Multiple mechanisms have been reported to be related to exercise capacity including diastolic and systolic cardiac function, reflex, metabolic, vascular and muscular response (3). Sexual satisfaction is an important component that influences quality of life in HF patients. Erectile dysfunction (ED) affects 60 to 70% of HF clinic outpatients (4). Symptoms, hormonal abnormalities, hemodynamic status, medication side effects and psychological factors are the major contributors to this sexual disorder.

In the physiopathology of chronic HF, the neurohormonal hypothesis for progression of heart failure has been considered of greater interest than the original hemodynamic mechanisms (5). Activation of sympathetic nervous system, renin-angiotensin-aldosterone system, arginine vasopressin, and endothelins are considered as neurohormonal targets in the treatment of HF. However, other hormonal abnormalities have been reported in HF such as significant decrease in growth hormones, insulin-like growth factor I and testosterone concentrations (6). The hormonal and cytokine activation contributes to peripheral muscle tissue wasting as well as anabolic/catabolic imbalance (7). In men, testosterone seems to play a role in determining anabolic function, anti-inflammatory and vasodilator processes. No data has been reported as regards testosterone's effect on hemodynamics, cardiac function and exercise capacity in HF patients with ED.

The aim of this study was to evaluate the correlation between serum testosterone levels and cardiac function, hemodynamics, and exercise capacity in HF patients with ED. In addition, we determined a HF hormone profile: serum levels of prolactin, luteinizing hormone, follicle-stimulating hormone, resting norepinephrine, and thyroid hormones.

MATERIALS AND METHODS

Studied Population

Fifteen randomized chronic male HF patients, 50 ± 10 years with ED (Table-1) for at least four months, in a steady relationship and presenting interest in sex were included. ED was defined as the inability to achieve or maintain a durable erection to permit satisfactory sexual intercourse (the 5th-item of the International Index of Erectile Dysfunction) (8,9). Patients were in stable clinical condition for three months without testosterone replacement or drugs that could have affected testosterone levels, as finasteride, opiates, glucocorticoids and anticonvulsants. All patients were sedentary and did not have heavy alcohol consumption, nephrotic syndrome or liver cirrhosis history. All patients were evaluated for ED etiology such as arterial insufficiency, venous leakage or penile fibrosis. No etiology was found, except HF syndrome. The protocol was approved by the Ethical Committee of the Heart Institute. Subjects provided written informed consent before participation. Exclusion criteria: ED secondary to causes other than HF, previous ED therapy, recent use of phosphodiesterase inhibitors, psychiatric or psychological disorders, unstable angina or recent myocardial infarction, syncope, high-risk arrhythmias, disease with limitation for exercise except HF, and symptomatic hypotension or systolic blood pressure (SBP) < 85 mm Hg.

Exercise Protocol

We measured systolic blood pressure (SBP) and diastolic blood pressure (DBP) with the patient in an upright position immediately before each exercise test, at the last minute of the six-minute walking test (6'WT), at maximum exercise peak, and at 1-minute recovery (10). Electrocardiography was continuously monitored. Pulmonary ventilation and gas exchange data were determined on a breath-by-breath basis with a computerized system (model Vmax 229 Sensormedics). The six-minute walking test (6'WT) was performed using a programmable treadmill without inclination and with patient-controlled speed (Series 2000, Marquette Electronics) at least 2 hours after a light meal and with controlled room temperature (21°C to 23°C). The patients were oriented to walk according to Borg's scale, with exertion level ranging from light to somewhat hard, from 11 to 13. After return of heart rate (HR), SBP, DBP, and symptoms to basal condition, patients underwent a progressive exercise test using a modified Naughton protocol. They were encouraged to perform maximum exercise until exhaustion or the onset of non tolerated symptoms occurred and the respiratory exchange ratio exceeded 1.0. The peak oxygen consumption (peak VO_2) was considered the maximum reached VO_2 value.

Cardiac Function and Hormonal Determinations

The right ventricular and left ventricular ejection fraction (RVEF and LVEF, respectively), as a percentage, were determined by echocardiogram. Hormonal dosage at rest before the exercise test included determination of serum total testosterone (fluoroimmunoassay method), prolactin, luteinizing

Table 1 *– Characteristics of patients with erectile dysfunction.*

Characteristics of Heart Failure Patients	N of Patients (%) or Value
Etiology	
Ischemic	22
Chagasic	22
Idiopathic dilated cardiomyopathy	26
Hypertensive	26
Valvular	4
NYHA functional class	
II	83
III	13
IV	4
Diuretics	91
ACE inhibitor	67
Angiotensin II AT1 receptor antagonists	8
ß-Adrenergic receptor blocker	61
Spironolactone	61
Amiodarone	17
Isosorbide 5-mononitrate (40 mg)	9
Total cholesterol, mg/dL	203 ± 49
HDL cholesterol, mg/dL	46 ± 13
LDL cholesterol, mg/dL	130 ± 41
Triglycerides, mg/dL	155 ± 145
Duration of ED symptoms, months	24 ± 19
Duration of CHF symptoms, months	61 ± 49

Values are mean ± SD or n (%); ACE = angiotensin-converting enzyme inhibitor, CHF-symptoms = congestive heart failure; ED = erectile dysfunction.

hormone, norepinephrine and follicle stimulating hormone. The normal value of testosterone in this study was 200-950 ng/dL. Lipid profile assessment was total cholesterol, HDL cholesterol, LDL cholesterol, Triglycerides. Due to hormonal circadian rhythms, all these tests were performed in the same period (early morning).

Statistical Analysis

The descriptive analysis was presented as mean and standard deviation. The variables studied underwent the non-parametric Spearman test for correlation, considering $p < 0.05$ (SPSS Statistical Software for Windows version 11.5. Inc., Chicago, IL, USA).

RESULTS

All patients had total testosterone serum levels in the range for normal subjects (200-950 ng/dL). Four patients had prolactin serum levels below the normal range (2.5-11.5 ng/mL). One patient had hypothyroidism and the other hyperthyroidism. The cardiac function, left ventricular diameters, and hormonal values of patients are reported in Table-2. Table-3 shows the hemodynamic and exercise variables.

Table 2 – *Cardiac function, left ventricular diameters and hormonal values in patients with erectile dysfunction.*

Variables of Heart Failure Patients	Number of Patients or Value
LV ejection fraction (echo) %	23 ± 7
RV ejection Fraction (echo) %	28 ± 8
LV end-diastolic diameter (echo), mm	72 ± 16
LV end systolic diameter (echo), mm	58 ± 55
Hypothyroidism/hyperthyroidism	2 patients
Serum total testosterone, ng/dL (normal 200-950)	604 ± 203
Prolactin, ng/mL (normal 2.5-11.5)	4.2 ± 2.3
Luteinizing hormone, IU/L (normal 1.4-9.2)	3.6 ± 1.9
Follicle-stimulating hormone, IU/L (normal 1-12)	4.2 ± 2.8
Resting norepinephrine, pg/mL (normal 40-268)	448 ± 214

Values are mean ± SD or n (%); LV= left ventricular; RV= right ventricular.

Table 3 – *Hemodynamic and exercise variables.*

Variable	p Value
HR 6m	111 ± 105 bpm
SBP 6m	141 ± 133 mmHg
DBP 6m	74 ± 71 mmHg
HR max	134 ± 127 bpm
SBP max	138 ± 128 mmHg
DBP max	78 ± 74 mmHg
Distance 6m	0.20 ± 0.03 miles
Slope 6m	31.7 ± 7
VO_2 6m	11.9 ± 2.9 mL/Kg/min
Slope Max	34.3 ± 8.7
VO_2 Max	17.8 ± 3.9 mL/Kg/min
Time Max	12.3 ± 8 min

HR 6m = Heart rate at last six minutes at six minutes cardiopulmonary walking test; SBP6m = systolic blood pressure at last six minutes on 6m cardiopulmonary walking test; DBP6m = BP at last six minutes on 6m cardiopulmonary walking test; HRmax = Heart rate at peak on maximum cardiopulmonary test; SBP max = SBP at peak on maximum cardiopulmonary test; DBP max = DBP at peak on maximum cardiopulmonary test. Distance 6m = distance on 6m cardiopulmonary walking test; Slope 6min = slope VE/VCO_2 on 6m cardiopulmonary walking test; $VO_2$6min = Oxygen consumption at six minutes of 6m cardiopulmonary walking test; SlopeMax = Slope VE/VCO_2 at maximum cardiopulmonary test; VO_2Max = VO_2 peak at maximum cardiopulmonary test; Time Max = Total time at maximum cardiopulmonary test.

Correlation between Testosterone Serum Levels and Cardiac Diameters, Cardiac Function, and Hemodynamic Data

Left ventricle ejection fraction (r =- 0.69, p = 0.004) (Figure-1) and right ventricle ejection fraction (r =- 0.55, p = 0.03) (Figure-1) showed inverse correlation with testosterone levels. SBP, DBP and heart rate during MCT (maximum cardiopulmonary test) did not show any correlation with testosterone levels or any hormonal serum levels except for DBP during the 6´WT that correlated with testosterone (r =-0.66, p = 0.007) (Figure-2). Left ventricular end diastolic diameter and left ventricular end systolic diameter did not show any correlation with testosterone levels either (Table-4)

Correlation between Hormonal Levels and Exercise Capacity Data

Exercise capacity variables on 6´CWT, VE/VCO_2 slope at six minutes, oxygen consumption at six minutes did not any show correlation with testosterone levels or hormonal serum levels. Only maximum distance at 6´CWT showed correlation (r = 0.50, p = 0.047) with testosterone levels. Also during the MCT, maximum VE/VCO_2 slope, maximum oxygen consumption and time of maximum test did not show correlation either (Table-4)

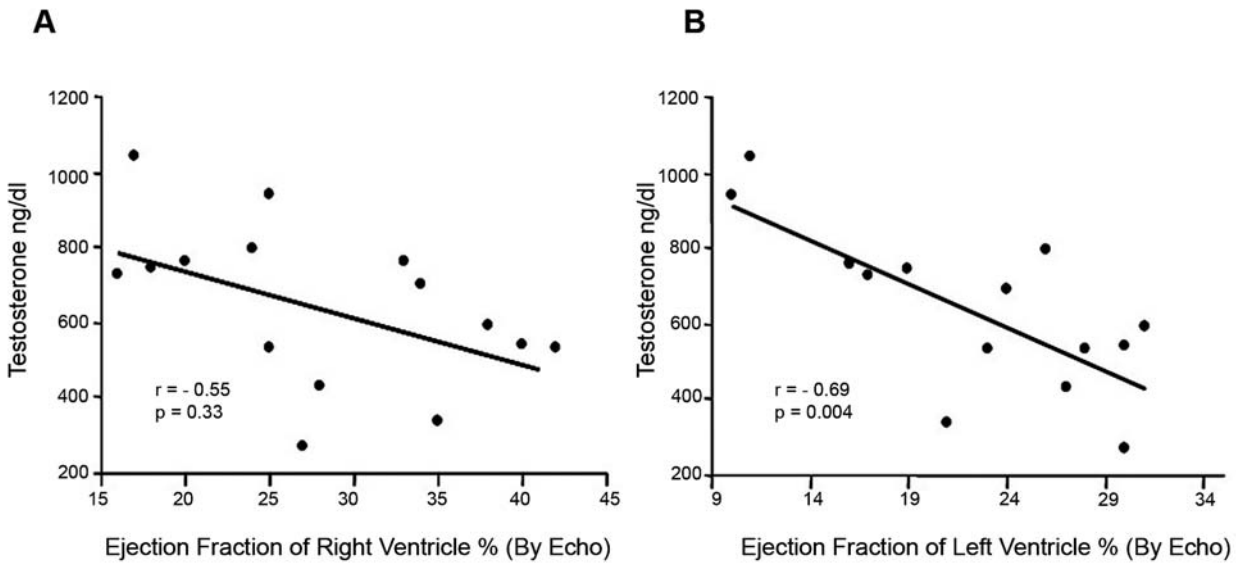

Figure 1 – *A) Regression linear plots in all patients between total testosterone and right ventricular ejection fraction (%, by echography). B) Regression linear plots in all patients between total testosterone serum levels and left ventricular ejection fraction (%, by echography).*

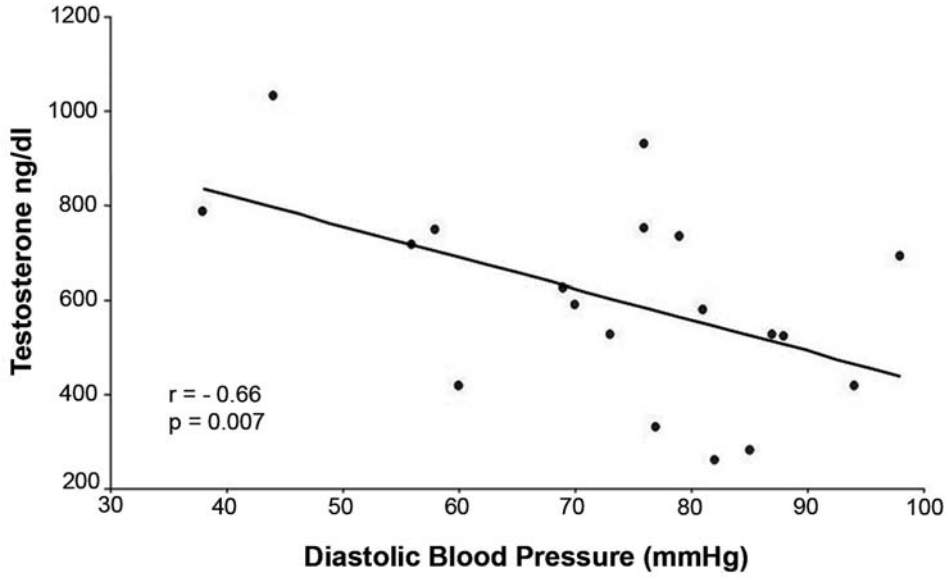

Figure 2 – *Regression linear plots in all patients between total testosterone serum levels systemic diastolic blood pressure at the last minute of the 6 minutes walking test.*

Table 4 *– Linear regression results between total testosterone serum levels and cardiac function, and exercise variables.*

Variable	r	p Value
LVEF (in %)	- 0.69	0.004
RVEF (in %)	- 0.55	0.03
LVEDD (in mm)	- 0.02	ns
LVESD (in mm)	0.04	ns
HR 6m	0.10	ns
SBP 6m	0.16	ns
DBP 6m	- 0.66	0.007
HR max	- 0.04	ns
SBP max	0.16	ns
DBP max	- 0.14	ns
Distance 6m	0.50	0.047
Slope 6m	- 0.11	ns
VO_2 6m	0.24	ns
Slope Max	- 0.21	ns
VO_2 Max	0.02	ns
Time Max	0.00	ns

LVEF = Means left ventricular ejection fraction; RVEF = Right ventricular EF; LVEDD = LV end diastolic diameter; LVESD = LV end systolic diameter; HR 6m = Heart rate at last six minutes at six minutes cardiopulmonary walking test; SBP6m = systolic blood pressure at last six minutes on 6m cardiopulmonary walking test; DBP6m = BP at last six minutes on 6m cardiopulmonary walking test; HRmax = Heart rate at peak on maximum cardiopulmonary test; SBP max = SBP at peak on maximum cardiopulmonary test; DBP max = DBP at peak on maximum cardiopulmonary test; Distance 6m = distance on 6m cardiopulmonary walking test; Slope 6min = Slope VE/VCO_2 on 6m cardiopulmonary walking test; $VO_2$6min = Oxygen consumption at six minutes of 6m cardiopulmonary walking test; SlopeMax = Slope VE/VCO_2 at maximum cardiopulmonary test; VO_2Max = VO_2 peak at maximum cardiopulmonary test; Time Max = total time at maximum cardiopulmonary test.

COMMENTS

Ours results demonstrated that there was an inverse correlation between right and left ventricular function and total testosterone serum levels in patients with ED. Other hemodynamic and exercise variables did not show a correlation with testosterone serum levels, except diastolic blood pressure and distance on 6'CWT. Other hormones abnormalities can be found in heart failure patients with erectile dysfunction.

Low testosterone levels were reported in severe stroke and acute myocardial infarction (11). In HF, the testosterone serum levels may be low or in the normal range depending of the severity of the disease (11). Also, it has been reported that plasma levels of dehydroepiandrosterone sulfate decreased in patients with chronic HF in proportion to the severity evaluated by marker of cardiac function (12). However, to our knowledge this is the first time that an inverse correlation was demonstrated between left and right systolic cardiac function and total testosterone serum levels in selected patients with HF and ED (6,13,14). It is also partially discordant that, after testosterone administration, serum total levels remained in the normal physiological range and no significant changes were found in BNP, TNF-α or LVEF. Also, there was also a positive correlation between testosterone and cardiac output (15). However, it was concordant with worsening of left ventricular remodeling with testosterone administration. The mechanisms to explain our findings are not clear. Effects of testosterone in the heart are controversial and alternative hypotheses could be proposed.

The first hypothesis is that the total testosterone serum blood levels could play a role in pathophysiology of HF, worsening cardiac function. This is concordant with the concept that anabolic steroids were considered as having cardiac toxicity with alterations of cellular pathology and organ physiology similar to those seen with heart failure and cardiomyopathy (16). In addition, testosterone treatment in very high supra-physiological doses causes myocardial hypertrophy and stiffening (17). Investigators administrated physiologic doses of testosterone and found an increase in the left ventricular diameters, but did not find any change in the LVEF (18).

The second hypothesis, in contrast is that testosterone serum levels could have beneficial effects on HF, and a resistance for testosterone could be proposed in selected HF patients (6). In rats, androgen therapy has been reported to improve coronary blood flow and increased both fractional shortening, thereby improving cardiac function. In addition, animal stud-

ies demonstrated vasodilator effects of androgens with potential beneficial effects in endothelial dysfunction (19), increment in IGF-1 levels with reduction in hyperinsulinemia and insulin resistance (20). In addition, resistance to growth hormone (GH) was also proposed in severe HF patients based on higher GH concentrations in proportion with low IGF-1 concentration (21). However, the hypothesis of testosterone resistance needs to be proved in future investigations including mediators, nongenomic and genomic androgen action mechanisms (10).

Our method to include these patients in this study could have influenced our results because of specific factors related to erectile dysfunction in HF and higher severity of our patients in comparison with other studies (18). Patients with HF may experience erectile dysfunction for similar reasons to the general population, however, there are social, psychological, physiological, and drug-related consequences specific to HF (22). However, the influence of ED in our patients should be considered if the concept that this symptom is a marker of severity of HF and endothelial dysfunction is accepted (23). Endothelial dysfunction appears to affect all cardiac and peripheral circulation. Significant relationship between sexual performance and functional class and six-minute walk test has been reported (24). Moreover, as suggested for GH resistance in more severe patients, our results could have been influenced by these factors.

The correlation between total testosterone and exercise capacity is concordant with previous randomized, double blind, placebo-controlled parallel trial of testosterone replacement therapy. Exercise capacity significantly improved with testosterone therapy, compared with placebo (18). There are evidences in animal studies that anabolic androgens attenuate muscle fatigue in response to exercise, although the mechanism has not been identified (25). In addition, androgens may have different effects on heart and peripheral muscle (15).

Our correlation between testosterone and exercise, systemic DBP is in concordance with vasodilator effect of testosterone, but previous reports have speculated that for a vasodilatation effect of testosterone supra physiological concentrations are required (26,27). However, beyond the vessel relaxation testosterone effect, this may activate the renin-angiotensin system (10,28). Also, vascular effects could be dose-dependent manner, with opposite effects according to the dose.

Despite previous reported improvement in New York Heart Association functional class and exercise capacity, the potential prescription of testosterone for HF should be evaluated. This potential prescription should consider our results and previous study that showed the increment of left diameters in HF patients after testosterone administration (17). Further investigations should be performed concerning elucidation of its action in the heart and to determine if it is safe. Acute hemodynamics, exercise and functional beneficial effects cannot guarantee a short and long-term benefit in cardiac function and primary endpoints for heart failure treatment (17,27).

Although this study is limited by the number of patients and did not include other markers of HF, nevertheless cardiac function could be considered as one of the main surrogate endpoints in heart failure. A better elucidation of testosterone mechanisms and action is warranted in a larger patient population.

CONCLUSION

Testosterone levels correlated directly with distance at six-minute cardiopulmonary walk test and inversely with diastolic blood pressure, right and left ventricle ejection fraction in heart failure patients with erectile dysfunction.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

Decreased testosterone level was reported throughout a 4-year follow-up in elderly patients with erectile dysfunction (ED) in addition to the association with an adverse metabolic profile (1). Testosterone deficiency is a common occurrence in men with chronic heart failure (CHF) and may underpin features of advanced disease, including reduced skeletal muscle mass and fatigue (2). Testosterone is known to act as a vasodilator in systemic, coronary and pulmonary vascular beds, as well as having anabolic properties (3). This effect could potentially lead to increased cardiac output and improved cardiovascular function that may contribute to the clinical benefit. Therefore, administration of testosterone to men with chronic congestive heart failure may lead to hemodynamic alterations. Furthermore, testosterone deficiency is positively correlated with cardiac output and exercise capacity in patients with CHF, whereas a significant improvement in both these parameters has been observed following testosterone replacement therapy. Testosterone therapy has also been shown to reduce circulating levels of inflammatory markers, (TNF-α and IL-1β) in patients with established coronary artery disease and testosterone deficiency (4).

Although the mechanisms are poorly understood, the improvement in exercise capacity was

shown to be positively correlated with the increase in serum testosterone level and was accompanied by a small increase in internal left ventricular length (2). As testosterone is a vasodilator, this could explain its anti-ischemic effects on cardiac function during exercise. However, it is currently unknown whether the vasodilatory effects of testosterone can influence the fatigability of skeletal muscle in a similar fashion. Therefore, adjunctive testosterone therapy might augment the positive effects of exercise rehabilitation on these clinical outcomes in hypogonadal males with stable CHF.

Currently, the main drawbacks in the design of clinical protocols and the inclusion of patients for the study of hormonal alteration lie in establishing the best assay for T measurement and in defining a baseline T cut off level. Although some limitations of the current study have been mentioned by the authors, the important feature of this study is that it addresses one timely and important issue, which is the correlation between serum testosterone levels and cardiac function, hemodynamic, and exercise capacity in HF patients with ED.

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EDITORIAL COMMENT

In this study Bocchi, and his colleagues documented that testosterone (TT) levels correlated directly with distance at six-minute cardiopulmonary walk test and inversely with diastolic blood pressure, right and left ventricle ejection fraction in heart failure patients with erectile dysfunction (ED). Erectile dysfunction is considered an early sign of endothelial dysfunction and hence cardiovascular disorders while low TT levels are related to ED.

TT level is considered a marker of vascular reactivity and non-traditional risk factor (Bio Marker) for coronary artery disease and peripheral arterial disease. It is also related to low arrhythmia threshold and prolonged QT intervals.

Low TT level is a predictor of cardiovascular mortality, and marker of low exercise tolerance and poor quality of life. So if used as an adjuvant in treatment of heart failure it may significantly improve the functional capacity and symptoms of heart failure.

Although the number of cases in this study is limited, as stated by the authors, the paper is interesting not only to the Urologist and Andrologists

but also to the cardiologist and general physicians. However, 61% of men included in this study were taking spironolactone, which is an anti-androgen rendering interpretation of the data a little bit difficult. Understanding the correlation between TT and cardiac functions will have a great beneficial effect on ED patients with heart failure.

Further studies using cardiac speckle technique and tissue Doppler imaging can provide more accurate assessment of cardiac function and perhaps demonstrate a correlation between TT levels and cardiac function.

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Surgical Technique

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Congenital Megaprepuce: A New Alternative Technique for Surgical Correction

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ABSTRACT

Objective: To present a new alternative technique for surgical treatment of congenital megaprepuce.
Materials and Methods: From April 2004 to April 2006, five patients aged 2 to 5 years were treated using the new technique. The technique is described and illustrated. It differs from other techniques in that it takes into consideration the constant ballooning of the foreskin, which gives to the external genitalia the aspect of a penoscrotal transposition. Cosmetic and functional success were also assessed by a case review.
Results: After a follow-up of 1 to 3 years, all patients have normal voiding and a satisfactory cosmetic aspect.
Conclusion: This new technique could be a useful alternative in treatment of the congenital megaprepuce.

Key words: *penis; children; foreskin; congenital abnormalities; surgery*
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INTRODUCTION

Congenital megaprepuce is a malformation consisting of a great redundancy of the inner preputial skin over a normal penile shaft and glans. The prepuce is not retractable and a ballooning of the foreskin is produced during the micturition. It was first described by O'Brien et al., in 1994 (1), and, since then, other authors have shown that although a rare condition, it is often confused with buried, trapped, concealed, webbed or micropenis (1-3).

The exuberant inner prepuce closed by the preputial ring creates a reservoir with a large dimension, leading to the anatomical aspect of penoscrotal transposition (Figure-1 and 2). Compression of the penile shaft results in urine spillage (Figure-3). The diagnosis is made, therefore, essentially by physical examination, which does not require functional exploration (4).

The objective of this report was to present a new alternative surgical technique that takes in account the penoscrotal transposition aspect of the malformation, which permits a satisfactory cosmetic appearance.

MATERIALS AND METHODS

From April 2004 to April 2006, five patients, aged 2 to 5 years, were treated using the technique.

The initial skin incision is shown in Figure-4. Then two traction stitches are made in the ventral point of the preputial ring, disassembling the foreskin and penile shaft, transforming the broken line incision in a

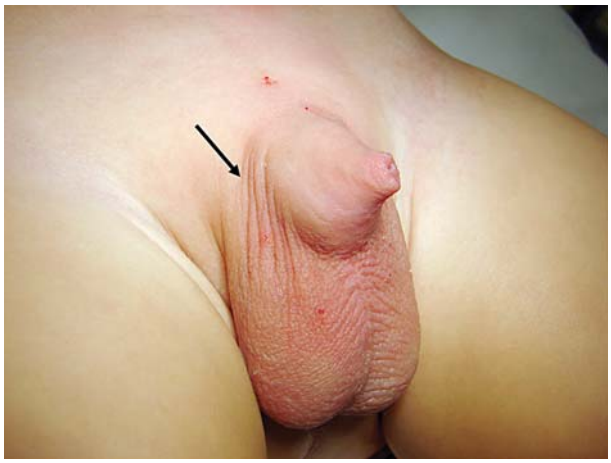


Figure 1 *– The arrow shows an aspect of penoscrotal transposition in a patient with megaprepuce.*

vertical straight line, as shown in Figure-5. The inner preputial skin is partially resected (Figure-6) and the foreskin is incorporated into the penile shaft with no flap required (Figure-7 and 8).

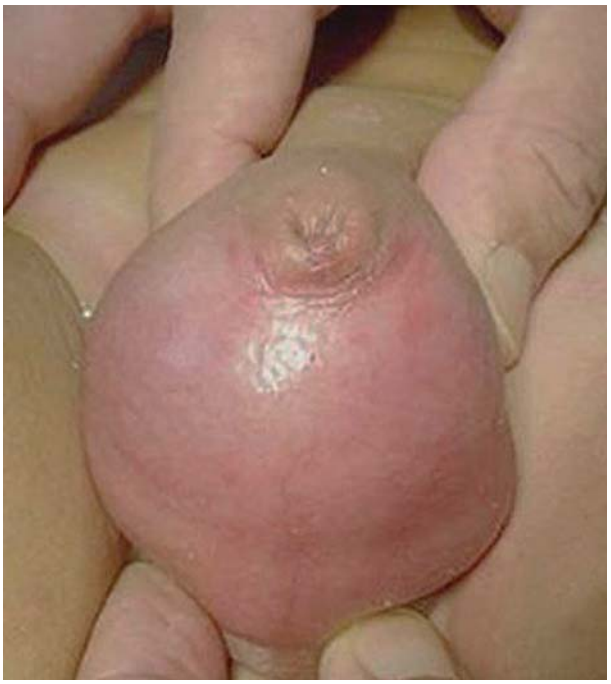


Figure 2 *– Typical penoscrotal ballooning of the congenital megaprepuce.*

RESULTS

All patients presented with the diagnosis of buried penis and 4 out of 5 have had repeated urinary tract infections. After the surgical treatment all patients have normal voiding pattern and the cosmetic aspect was considered adequate 1 to 3 years after surgery (Figure-8 and 9).

COMMENTS

Congenital megaprepuce was first described by O'Brien et al. (1). It is caused by a redundant inner prepuce over a preputial ring, which is not retractable, leading to a ballooning of the foreskin. Chronically it creates a reservoir, which renders the external genitalia an aspect of a penoscrotal transposition.

In agreement with other authors we believe that the condition is almost always confused with buried, trapped, concealed, webbed or micropenis. We postulate, however, that other previously reported surgical techniques have not considered the penoscrotal aspect of the genitalia, chronically distended by the accumulation of urine (1-6) (Figures-2 and 3).

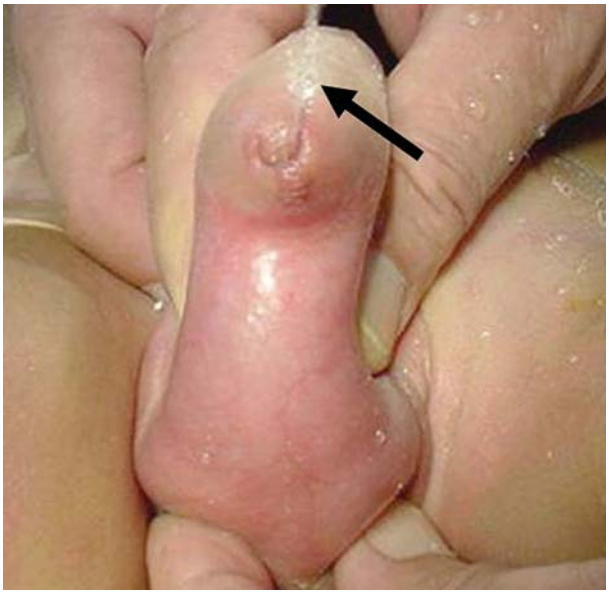
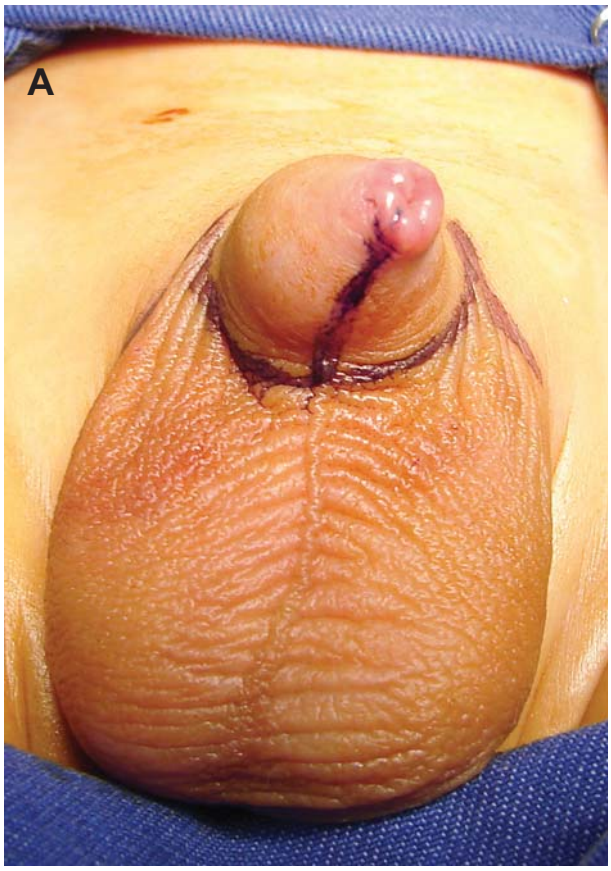


Figure 3 *– The arrow shows the urinary jet flow when the foreskin is squeezed.*



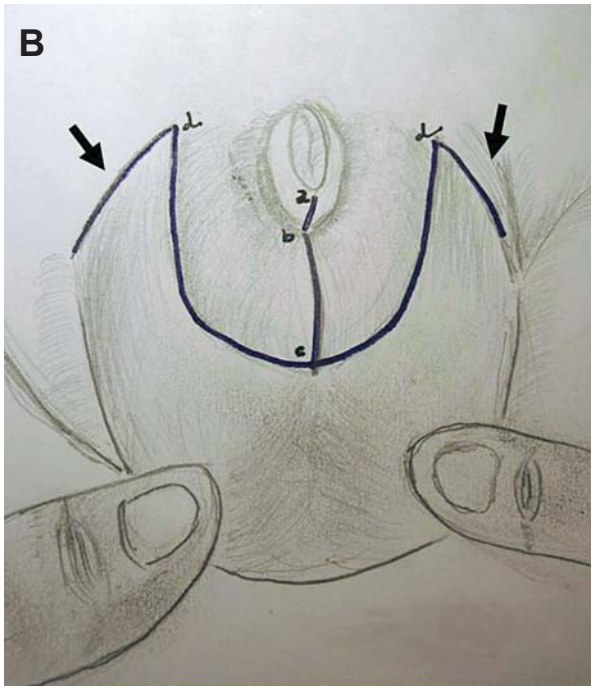


Figure 4 – *A) Correction o penoscrotal transposition. B) Schematic drawing. Arrows show the lateral incisions.*

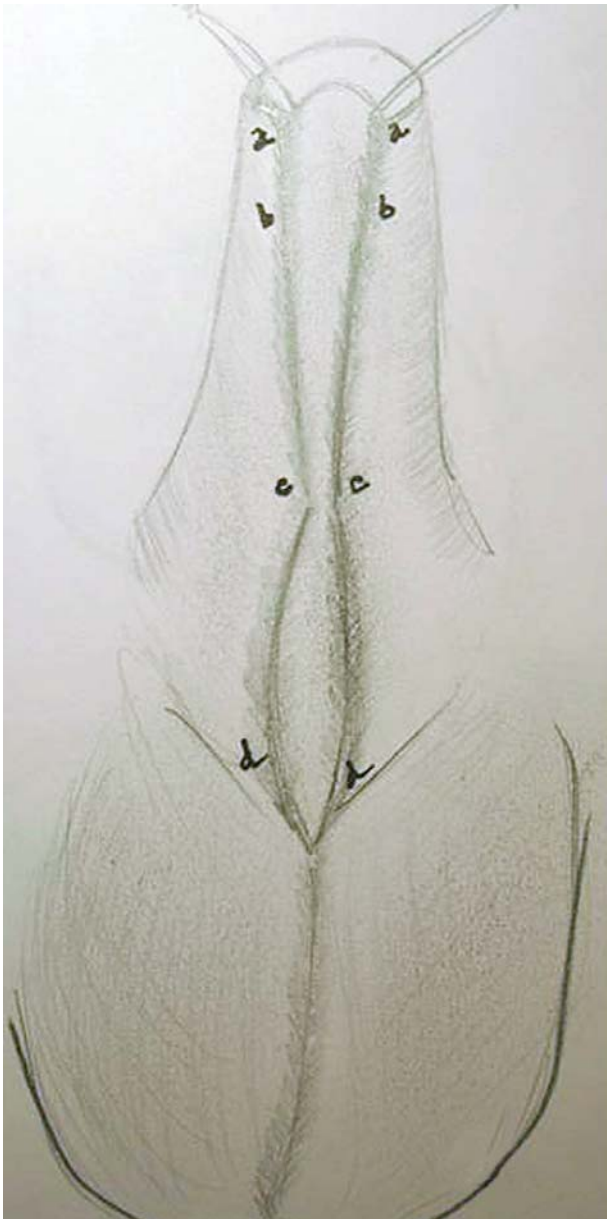


Figure 5 – *Traction in the ventral preputial ring changing the broken incision into a strait line.*

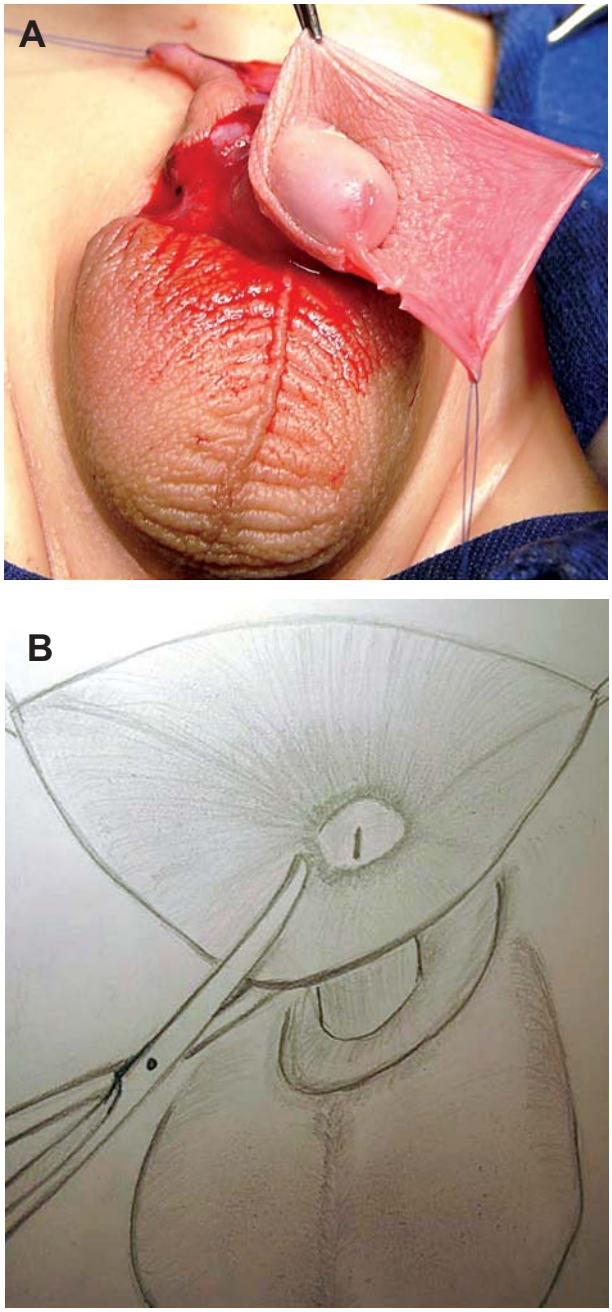


***Figure 6** – A) Cutting the inner prepuce. B) Schematic drawing.*

Unlike other published series all our patients but one presented with a urinary tract infection (1-7).

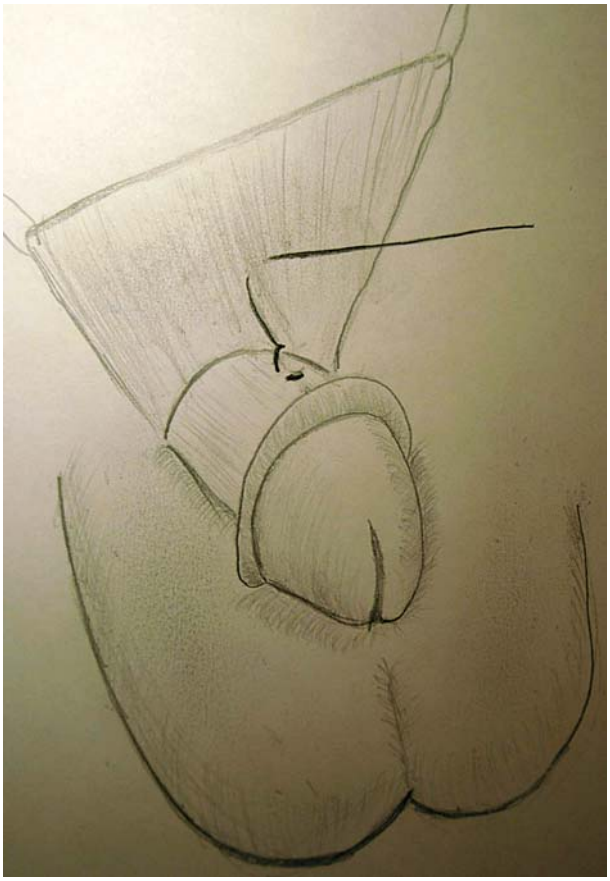
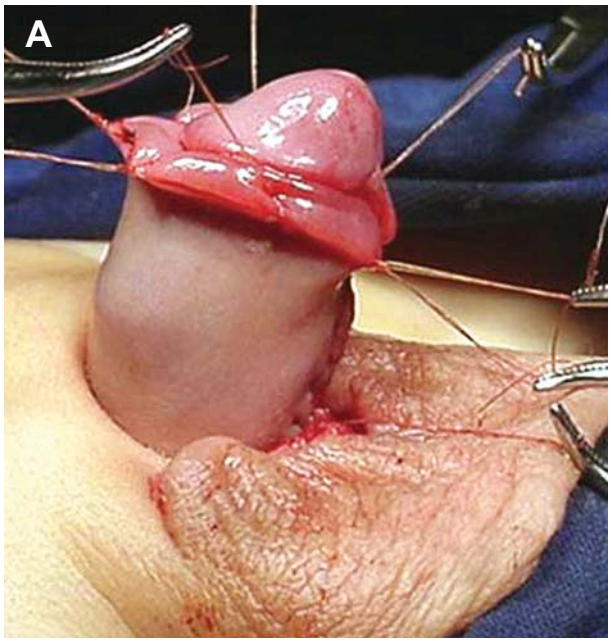


***Figure 7** – Stitches incorporate the foreskin to the penile shaft.*

As reported by Summerton et al. (3) we disagree with Popis and Crapp (7) that early circumcision cures the problem because this would remove the basic skin required to resurface the penile shaft.

The surgical technique presented in this study is aimed at correcting the penoscrotal transposition in addition to the resection of the redundant inner prepuce.

Although the present series included only five patients, we believe, as in the series of Summerton et al. (3), that when the immediate postoperative aspect is cosmetically treated, the long term results will be satisfactory



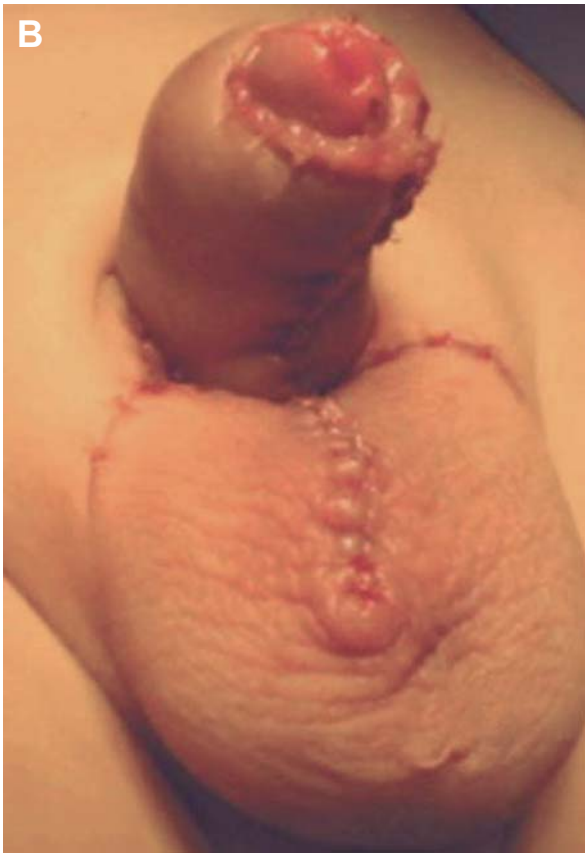


Figure 8 – *A) and B) Postoperative surgical aspect.*

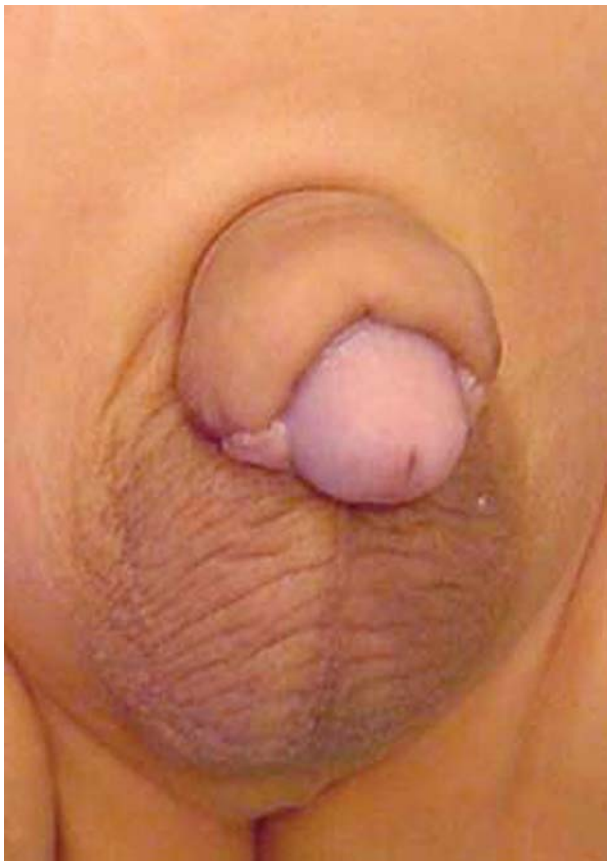


Figure 9 – *Postoperative aspect 18 months after surgical correction.*

CONFLICT OF INTEREST

None declared.

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Successful Treatment of Unilateral Cryptorchid Boys Risking Infertility with LH-RH Analogue

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ABSTRACT

Introduction: Infertility is the primary concern for boys with uni- or bilateral undescended testes. An early and seemingly successful orchiopexy does not improve fertility in a substantial number of cryptorchid males. We confirmed that LH-RH analogue (LH-RHa) treatment induces an increase in and maturation of the germ cells; however, it was uncertain if treatment would improve the chance of fertility later in life.
Materials and Methods: Thirty unilateral cryptorchid boys, with an average age of 3 years at the time of surgery, were included in the study. Testicular biopsy showed that they had impaired testicular maturation and were therefore at high risk for infertility. Fifteen of the 30 unilateral cryptorchid boys were treated with 10 µg LH-RHa (Buserelin) nasal spray, administered on alternate days for a period of 6 months, following orchiopexy. The control group consisted of 15 cryptorchid boys who had been treated by Schoemakers type of orchiopexy, alone. After puberty, the ejaculates of both groups were analyzed.
Results: All males in the untreated group were severely oligospermic, with 20% being azoospermic. In contrast, 86% of the treated ex-cryptorchid males had a sperm concentration within the normal range; this was significantly different from the sperm concentration found in the untreated group ($p = 0.000008$).
Conclusion: For the first time, we demonstrate that infertility in cryptorchidism can be successfully corrected when suitably treated with a LH-RHa. Sperm parameters normalized following therapy in the majority of cryptorchid males who, untreated, would have remained infertile. This innovative hormonal treatment will have a profound effect on the current recommended surgical treatment of boys with undescended testes.

Key words: *cryptorchidism; sperm; Ad spermatogonia; fertility; LH-RH analogue; treatment*
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INTRODUCTION

Cryptorchidism is the most common urogenital birth-defect in males, necessitating surgery in about 27,000 boys each year in the United States (1). Since 1960, when Charny stated that "the surgical techniques currently practiced by most surgeons must improve significantly, albeit the cosmetic results are arguably better but the functional results fall far short of the intent" very little has changed (2). Although the effect on testicular development and fertility has been studied extensively since that time, there is only one general consensus: untreated boys with bilateral undescended testes will be infertile.

In 1975, Ludwig and Potempa found that the fertility rate is inversely proportional to the age of the patient at the time of surgery. Consequently, it was expected that infertility resulting from cryptorchidism

could be cured if orchiopexy was performed before the second year of life (3). Thirty years later, when the fertility results of early surgery were obtainable, we realized that the therapeutic strategy to operate before the age of 2 years had not improved fertility hopes in a substantial number of cryptorchid patients (4). Cryptorchid boys lacking Ad spermatogonia will be infertile despite a seemingly successful orchiopexy at an early age (4). The main cause is impaired mini-puberty, the surge of gonadotropins and testosterone that occurs in early infancy (5). In an attempt to correct impaired mini-puberty, we administered a LH-RH analogue to cryptorchid boys following successful surgery and achieved an increase in the number of germ cells (6). We report the results of the first 15 patients treated with LH-RHa after successful surgery, who are now young adults, and compare the outcomes with patients who were treated with surgery only. The amelioration of testicular maturation appears to result in the normalization of excretory testicular function.

MATERIALS AND METHODS

Fifteen unilateral cryptorchid boys who had a Schoemakers type of orchiopexy between the ages of 1-6 years were subsequently treated with LH-RH. Their cryptorchid testes were located outside of the scrotum since birth. A vast majority had testes located inguinal or at external inguinal ring. Two patients, one of each in treated and untreated group had testes located in abdomen. Twelve out of 15 patients had an unsuccessful HCG treatment before surgery. Testicular biopsies were obtained during orchiopexy, fixed in 3% glutaraldehyde, and embedded in Epon. Semi-thin sections, 1 μ thick, were examined with light microscopy. At least 100 tubular cross sections were counted to estimate the total number of germ cells per testis. The entire biopsy was analyzed for the occurrence of Ad spermatogonia. All patients had < 0.2 germ cells per tubular cross section (normal > 2 per tubular cross section) and none had Ad (dark) spermatogonia. Therefore, these patients were at high risk of being infertile (7,8). Within 3 months following surgery, treatment with the LH-RH analogue Buserelin, a nonapeptide ethilamide of D-Ser $(Bu^t)^6$ LH-RH, was initiated, with 10 μg applied as an intranasal spray in the evening on alternate days for a period of 6 months. All patients had regular monthly check-ups during the course of treatment. The boys' mothers were questioned about compliance to the nasal spray treatment as well as possible adverse side effects of the medication. Furthermore, their general well being and genital status were estimated, including determining testicular volume, penile length with a ruler, and Tanner stage of sexual development.

These 15 patients, who are now young adults, were among the first to receive LH-RH analogue treatment at the ages of 1-6 years (average age, 3 years; 95% CI 2 - 4 years). They were recruited from a group of 19 who were invited to participate in the study, and were older than 18 years of age. None of the patients had additional surgeries or severe illness requiring hospitalization during the 15-19 years following treatment. Twelve of 15 were non-smokers and none was on chronic medication or was drug abusers. During a very recent medical check-up, their general status and Tanner stage of pubertal development was appraised. Testicular volume and the length of stretched penis were measured. Testicular volume was determined according to the formula; $V=4/3 \times \pi \times D/2 \times d^2$; $(0.71 \times D \times d^2)$. An ejaculate was collected following sexual abstinence for at least 5 days. Semen analysis was performed by computer-assistance and additionally confirmed with repeated microscopic examinations. In accordance with WHO standards, infertility was assumed if the sperm concentration was $< 40 \times 10^6$ per ejaculate (9). All patients with a sperm concentration within the infertile range had at least a second ejaculate analyzed within 2-4 weeks. The better sperm concentration of the 2 evaluations was included in the study. The majority (8/15) of patients had to deliver their sperm specimens by mail; therefore, sperm motility could not be evaluated. Nevertheless, sperm concentration, ejaculate volumes, and sperm morphology with teratozoospermic index were evaluated.

The age-matched control group was selected from 181 unilateral cryptorchid patients who had had their sperm ejaculates analyzed. Patients in the control group had all undergone a successful Schoemaker type orchiopexy and a testicular biopsy was obtained during the surgery; however, they did not

undergo additional LH-RH treatment. Fifteen of the 181 fulfilled the same criteria as the treated group and were included in the control group. They all had unilateral cryptorchidism, were the same age at treatment (average age, 4 years; 95% CI 2-6; $p = 0.35$), had no Ad spermatogonia, and had a total number of germ cells < 0.2 per tubule. 13 out of 15 patients had an unsuccessful HCG treatment prior to surgery.

Statistical Analysis

The recruitment of patients for this, non randomized, study was designed to be balanced. Given the customary values for the significance level $\alpha = 0.05$ and the power $\beta = 90\%$ and using the module "MTT1-1" in the software "nQuery Advisor" The sample sizes are determined to N = 12 for a one-sided and to N = 14 for the two-sided Wilcoxon/Mann-Whitney U-test.

Following assumptions were entered into the module "MTT1-1" of nQuery Advisor: That the mean sperm count in the treated group was larger than 40 millions whereas in the untreated group it was smaller than 10 millions where standard deviation was estimated to be smaller than 20 millions.

We therefore first analyzed the group of 181 ex-unilateral cryptorchid males who were only surgically treated and identified 15 who fulfilled the entry requirements for the study. Consequently, we invited our first 19 ex-unilateral cryptorchid males, who had LH-RHa treatment and were older than 18 years, to participate in the study. Fifteen of the first consecutive responders entered the study. The Mann-Whitney U test for unpaired data was used in the software package StatXact 6.30 (2004) from CYTEL Corporation. Nonparametric 95% confidence intervals for the medians were computed by bootstrapping.

Ethical Considerations

In accordance with the Helsinki declaration, the Institutional Review Board (IRB), and the Independent Ethics Committee of University Children's Hospital Basel approved all aspects of this study. In particular, approval was given for research involving the use of material (data, documents, records or specimens) that had been collected for non-research purposes.

RESULTS

The total number of germ cells in the surgery "only" group was an average of 0.02 germ cells per tubular cross section (95% CI: 0 - 0.2). This was the same as the number observed in the treated group, who had an average of 0 germ cells per tubular cross section (95% CI: 0.- 0.05; $p = 0.22$). Both groups had no Ad (dark) spermatogonia present in their entire testicular biopsies. Indicating defective germ cell transformation due to an impaired mini puberty.

There were no adverse side effects and no changes in the Tanner stage of pubertal development during the hormonal treatment.

Most often, mothers reported that their boys were more active than usual during treatment. Testicular volume remained unchanged compared with that before the treatment, while there was a significant increase in penile length from an average of 4.5 cm (95% CI 4-5) before treatment to an average of 5.0 cm (95% CI 4.5-6) after treatment ($p < 0.001$) (Table-1).

At a recent examination at an average age of 19 years (95% CI 18-22), all males were in a healthy condition. They all had Tanner V stage of sexual development and normal erectile function. The length of the stretched penis was in the lower normal limit with average length of 12 cm (95% CI 10-13 cm) (Table-2). Testicular volume of orchiopexy testes was less when compared with the contralateral descended partner; ex-undescended testicle 29 mL (95% CI 22.- 36 mL) vs. contralateral descended testicle 38 mL (95% CI 30-46 mL; $p < 0.0026$) (Table-2).

Spermiogram

In the surgery "only" group, all ex-cryptorchid males suffered severe oligospermia, and 20% (3/15) of the group had azoospermia. The average sperm concentration was 1×10^6 (95% CI: 0-13) per ejaculate (Figure-1), Table-3.

In the LH-RH treated group, one male had oligospermia and one had a diminished sperm concentration while in the remaining 13 males had a normal sperm concentration, (Table-2). Average total sperm concentration in the treated group was of 90×10^6 (95% CI: 53-164) per ejaculate (Figure-1). This was significantly different from the sperm concentrations

Table 1 *– Characteristics of the 15 patients with cryptorchidism immediately before and after treatment with luteinizing hormone releasing hormone.*

Patient	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
Age at surgery/ years	3	4	3	4	2	6	2	6	2	3	3	3	1	3	4
Cryptorchid testis	L	L	R	R	R	L	R	R	L	L	L	L	L	L	L
S/T (germ cells/ tubules)	0.04	0	0.02	0	0.1	0	0	0	0	0.02	0	0.03	0.05	0.06	0
Ad/tubule	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Testis volume before (mL)	1.8 L 1.8 R	1.7 L 1.8 R	1.2 L 0.8 R	1.9 L 2.1 R	1.1 L 1.1 R	2.1 L 1.0 R	1.0 L 1.0 R	2.0 L 2.0 R	1.8 L 1.8 R	1.5 L 1.5 R	1.0 L 1.0 R	1.0 L 1.2 R	1.3 L 1.2 R	1.4 L 1.2 R	1.2 L 2.0 R

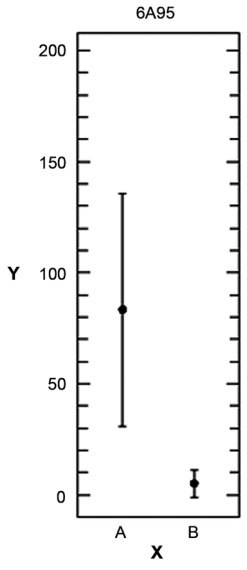

Figure 1 *– Sperm concentration/ejaculate in Buserelin treated group (A) and untreated group (B) Mean and SD are demonstrated. Y = number of sperm in million per ejaculate.*

in the surgery "only" group (p = 0.000008) (Figure-1). Furthermore, in the LH-RHa treated group, the teratozoospermic index and volume of ejaculates were in the normal range (Table-2). If fertility capacity were defined according to the Tygerberg strict criteria, then sperm morphologic pattern was distributed similar to the distribution found in the normal fertile population (10). Two males had P-pattern (poor-prognosis), 8 were in the G-pattern (good prognosis) group, and 5 were in the N-pattern (normal forms > 14%) group (Table-2).

COMMENTS

Attempting to improve the unfavorable fertility results through early treatment of cryptorchidism is generally recommended and accepted today. According to current thinking, hormonal, hormonal/surgical, or only surgical treatment should be completed before the patient's second birthday. However, boys with a severe reduction and im-

Table 2 *– Characteristics of the 15 patients with cryptorchidism initially treated with surgery and luteinizing hormone releasing hormone, at follow-up after puberty.*

Patient	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
Age at spermiogram	21	20	18	19	19	23	18	25	18	19	18	20	20	18	22
Testis volume (mL)	42 L 52 R	37 L 52 R	32 L 11 R	32 L 35 R	68 L 57 R	9 L 13 R	26 L 32 R	68 L 43 R	18 L 32 R	26 L 42 R	36 L 34 R	29 L 48 R	21 L 22 R	36 L 45 R	13 L 29 R
Penis length (cm)	12	12	12	13	13	10	11	14	9	14	12	10	13	12	12.5
Tanner stage genital development	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V
Sperm concentration	57	53	19	58	198	115	1	94	60	107	164	97	63	180	81
Normal morphology % (≥ 14%)	7	8	11	11	18	21	0	12	4	15	8	15	11	14	11
Teratozoospermic-index (< 1.8)	1.2	1.8	1.4	1.4	1.4	1.1	1.9	1.7	1.5	1.5	1.5	1.3	1.2	1.3	1.5
Volume ejaculate (mL)	4.5	6.3	1.5	1.9	4.1	4.6	1.2	2.8	2.5	3.2	2.8	4.9	4.6	4.5	7.0

paired transformation of germ cells regardless of the time of surgery, as well as uni- or bilaterality of cryptorchid gonads, were infertile (4,11). Therefore, whether or not the patient will achieve normal fertility following successful surgery depends mainly upon the presence of Ad spermatogonia at the time of orchiopexy (4,11). At least half of cryptorchid population undergoing surgery had no Ad spermatogonia and consequently were candidates for hormonal treatment (7). It is known that a testis in an intra-abdominal position has in general bad testicular histology beyond one year of age, and that a testis in pre-scrotal position has a better or is more close to normal testicular histology (8,11). However, in all positions, although with different incidences, the testes with no Ad spermatogonia and < 0.2 germ cell per tubule could be observed. Thus, the histological findings distinguished those patients who specifically required additional treatment than testicular position at surgery, albeit the fact that 90% of boys with intra-abdominal testes probably require hormonal treatment. In this study only two patients; one of each group had their testis located in the abdomen, therefore the study is comparable also with regard to testicular position found at surgery. In male gonadotropin secretion which increases from 2 to 4 months after birth stimulating Leydig cells to secrete testosterone (12-14). Testosterone increase is blunted in cryptorchid boys (13,14). This insufficient testosterone secretion is responsible for impaired transformation of gonocytes into Ad spermatogonia (4,5,11,15-17). Additional rationale for LH-RHa treatment was based on the histological analyses of undescended testes in infancy (4,5,11,15-20).

Table 3 – *Characteristics of the 15 patients with cryptorchidism initially treated with surgery at follow up after puberty.*

Patient	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**
Age at surgery/years	2	2	3	2	5	6	4	5	6	5	4	6	6	< 1	2
S/T (germ cells/tubules)	0.2	0	0	0	0.2	0.01	0.04	0.01	0	0.02	0.1	0	0.1	0.2	0.04
Ad/tubule	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Age at spermiogram	20	19	21	20	25	18	22	23	25	24	20	21	23	24	20
Tanner stage genital development	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V
Sperm concentration/ ejaculate	0	1	6	14	0.1	2.2	18	9	0.1	13	2	0.1	13	0	0
Normal morphology (≥ 14%)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Volume ejaculate (mL)	3.8	5	2.9	3	4.2	5	5.2	5	4.2	5.1	8.2	3.8	5	4.5	4.6

The LH-RH analogue (Buserelin) given on alternate days for a period of five months in a previous study caused no inhibition of gonadotropin secretion (21). Moreover, LH values determined in the first morning urine were higher at the end of the treatment (21). Six months LH-RHa treatment increased the number of germ cells in cryptorchid testis (7,21). This increase was age dependent (7). The best results were achieved if the cryptorchid boys were treated before the age of seven years, implying that successful treatment of impaired mini-puberty should be performed before this age.

In 1997, we presented results of fertility outcome in cryptorchid boys who were treated with a LH-RH analogue at the age of 8 years and older. Compared with surgery as the only treatment, a significant amelioration, but not normalization, of sperm concentration was achieved in the treated group (22). This result showed that LH-RHa treatment had a lasting effect upon spermatogonial development.

Table 4 – *Characteristics of genitalia in boys treated with LH-RHa before and after treatment.*

Testicular Volume (mL)	**Before Treatment**	**After Treatment**	**p Value**
Cryptorchid testis	1.4 (95%CI;0.8-2.1)	1.2 (95%CI;1-3.2)	0.65
Descended testis	1.2 (95%CI;1-3.2)	1.4 (95%CI;1-2.5)	0.52
Penis length (cm)	4.5 (CI;4-5)	5.0 (95%CI;4.5-6)	< 0.001

Table 5 – *Summary of characteristics.*

	LH-RHa Treatment	Surgery "Alone"	p Value
Age at surgery (year)	3 (95%CI;2-4)	4 (95%CI;2-6)	= 0.35
S/T at surgery	0 (95%CI;0-0.05)	0.02(95%CI;0-2)	= 0.22
Ad spermatogonia at surgery	0	0	
Age at spermiogram (year)	19 (95%CI;18-22)	21 (95%CI;18-25)	< 0.02
Sperm count/ejaculate (mio)	90 (95%CI;53-164)	1.0 (95%CI;0-13)	= 0.000008
Normal morphology	11% (95%CI;0-21)	0	
Ejaculate volume (mL)	4.1 (95%CI;1.2-7)	4.6 (95%CI;2.9-8.2)	= 0.074

To analyze the efficacy of the LH-RHa (Buserelin) treatment in boys younger than 7 years, we treated unilateral cryptorchid patients with a high infertility risk according to their testicular histology. The recruitment of patients for this study was designed to be balanced [see statistics section]. From 181 ex-unilateral cryptorchid males who were only surgically treated [representing entire group studied] 15 patients fulfilled the entry requirements for the study. Consequently, we invited our first 19 ex-unilateral cryptorchid males, who had LH-RHa treatment and were older than 18 years, to participate in the study. Fifteen of the first consecutive responders entered the study Spermiogram results showed that 13 of 15 unilateral cryptorchid males had a normal sperm concentration. In addition, the distribution of the fertility patterns of the sperm morphology was identical to that of the normal fertile population (10). Furthermore, in those males with a P-pattern morphology, an excellent sperm concentration will compensate, with a significantly better chance of inducing pregnancy (23). Normalization of the sperm concentration in 86% of unilateral cryptorchid males, who were in the high risk group for developing infertility, profoundly changes our current concept of cryptorchidism treatment. For the first time, it is possible to demonstrate that infertility caused by cryptorchidism that was believed to be a congenital malformation can be successfully corrected if adequately treated.

In conclusion, infertility induced by cryptorchidism is an endocrine disease of impaired minipuberty. Treatment with a LH-RHa before the age of six years following a successful orchiopexy resulted in the normalization of sperm parameters in the vast majority of patients. Since not all patients with unilateral cryptorchidism belong to the infertility risk group, some will profit from early surgery without need for subsequent LH-RHa treatment. Testicular biopsy is the only diagnostic procedure capable of identifying patients who need to be treated with LH-RHa following successful surgery. Because of its important prognostic value, a testicular biopsy should be routinely performed during the orchiopexy.

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CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

The present study reinforce the concept that cryptorchidism is resultant of hormonal alteration that affect both testes, even when the alteration is unilateral.

The study design evidences that the mere relocation of an ectopic gonad in the correct anatomic position is not enough to grant future fertility.

Hormonal therapy for cryptorchidism was confused with an alternative therapy for surgery. Nevertheless, the main objective of the hormonal therapy is to improve the histological quality of the gonad, improving future fertility rates.

This study indicates that hormonal therapy acts synergically with surgery for obtaining nearly normal fertility rates in the future.

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EDITORIAL COMMENT

Cryptorchidism is one of the most common congenital pathologies in boys. Treatment of this congenital anomaly concerns the possibility of diminishing risk of malignant degeneration and improving fertility. Surgery is the best treatment for cryptorchidism but there are many studies showing good results for testicular migration after therapy with hCG or with GnRH (1-3). The evidence for the use of hCG vs. GnRH shows advantages for hCG, and a recent review also shows that there is evidence that luteinizing hormone releasing hormone (LH-RH) is more effective than placebo (4) The hormonal treatment in cryptorchidism is controversial. Considering the efficacy and the possible side effects of the hormonal treatment a recent meta-analysis recommended that the hormonal treatment of cryptorchidism could not be further recommended (5). An experimental study shows that hCG impairs the seminiferous tubule histology in normal testes of rats (6). There is still controversy on whether it may be useful as an adjunct to surgery to stimulate germ cells. Current evidence suggests that hormonal therapy may not stimulate transformation of neonatal gonocytes but may trigger prepubertal mitosis of primary spermatocytes (7). Subfertility is considered the main consequence of cryptorchidism even after timely orchiopexy. Gonadotropin-releasing hormone (GnRH) treatment appears to improve fertility later in life by inducing germ cell maturation. A recent paper shows that neoadjuvant GnRH treatment improves fertility index in prepubertal cryptorchidism (8). The great contribution of this paper is the evaluation of seminal parameters in patients that was submitted to orchiopexy with hormonal treatment in childhood. This paper tends

to confirm the beneficial effects of medical treatment after orchiopexy in patients with high risk of infertility confirmed by testicular biopsy. One important conclusion of this paper is that testicular biopsy should be performed routinely to evaluate testicular histology during surgery in patients with cryptorchidism.

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Laparoscopic Diagnosis and Treatment of Nonpalpable Testis

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ABSTRACT

Introduction: Treatment of the cryptorchid testicle is justified due to the increased risk of infertility and malignancy as well as the risk of testicular trauma and psychological stigma on patients and their parents. Approximately 20% of cryptorchid testicles are nonpalpable. In these cases, the videolaparoscopic technique is a useful alternative method for diagnosis and treatment.

Materials and Methods: We present data concerning 90 patients submitted to diagnostic laparoscopy for impalpable testicles. Forty-six patients (51.1%) had intra-abdominal gonads. In 25 testicles of 19 patients, we performed a two stage laparoscopic Fowler-Stephens orchiopexy. The other 27 patients underwent primary laparoscopic orchiopexy, in a total of 29 testicles.

Results: We obtained an overall 88% success rate with the 2 stage Fowler-Stephens approach and only 33% rate success using one stage Fowler-Stephens surgery with primary vascular ligature. There was no intraoperative complication in our group of patients. In the laparoscopic procedures, the cosmetic aspect is remarkably more favorable as compared to open surgeries. Hospital stay and convalescence were brief.

Conclusions: In pediatric age group, the laparoscopic approach is safe and feasible. Furthermore, the laparoscopic orchiopexy presents excellent results in terms of diagnosis and therapy of the impalpable testis, which is why this technique has been routinely incorporated in our Department.

Key words: *testis; cryptorchidism; laparoscopy*
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INTRODUCTION

Cryptorchidism is the most common genitourinary anomaly in male children. Its incidence can reach 3% in full term neonates, rising to 30% in premature boys (1). The treatment of the cryptorchid testicle is justified by the increased risk of infertility and malignancy, as well as an associated inguinal hernia and the risk of trauma to the ectopic testicle against the pubis. Furthermore, the psychological stigma of a missing testis for the patient, as well as the parents' anxiety are also factors that justifies this type of treatment (2,3).

About 20% of cryptorchid testicles are nonpalpable. In these cases, the laparoscopic technique is a useful alternative method of diagnosis and treatment. We assessed our data and present our results, including a comparison between the laparoscopic and two stage Fowler-Stephens approaches.

MATERIALS AND METHODS

Between September 1994 and September 2005, 90 patients were submitted to diagnostic laparoscopy for impalpable testicles. Of these, 34

(37.8%) presented with bilateral, while 56 (62.2%) had unilateral impalpable cryptorchidism. The age and the laterality are presented in Table-1.

Preoperatively, all the patients were examined at least by two different examiners at different times, confirming the diagnosis. Another careful physical examination was performed in the operating room, with the patient under anesthesia. When the testicle was palpated on any one of these occasions, the patient was submitted to an open orchiopexy.

Although the preoperative ultrasound for location of the testicle was performed in some patients, with negative results in all, no patient underwent computerized tomography scan or magnetic nuclear resonance imaging for the same purpose.

There was no age limit for the laparoscopic procedure. The procedure was performed under general anesthesia, with orotracheal ventilation and nasogastric and vesical tubes.

Table 1 *– Age and laterality data.*

Total patients	90
Age	11 months - 22 years (mean 6.4 years)
Number of testes (total)	124
Bilateral	68
Right side only	20
Left side only	36

The laparoscopic technique (Figure-1) has previously been described (4-6).The laparoscopic findings were similar to those described by Castilho in 1990 (7), and are summarized in Table-2. Surgical

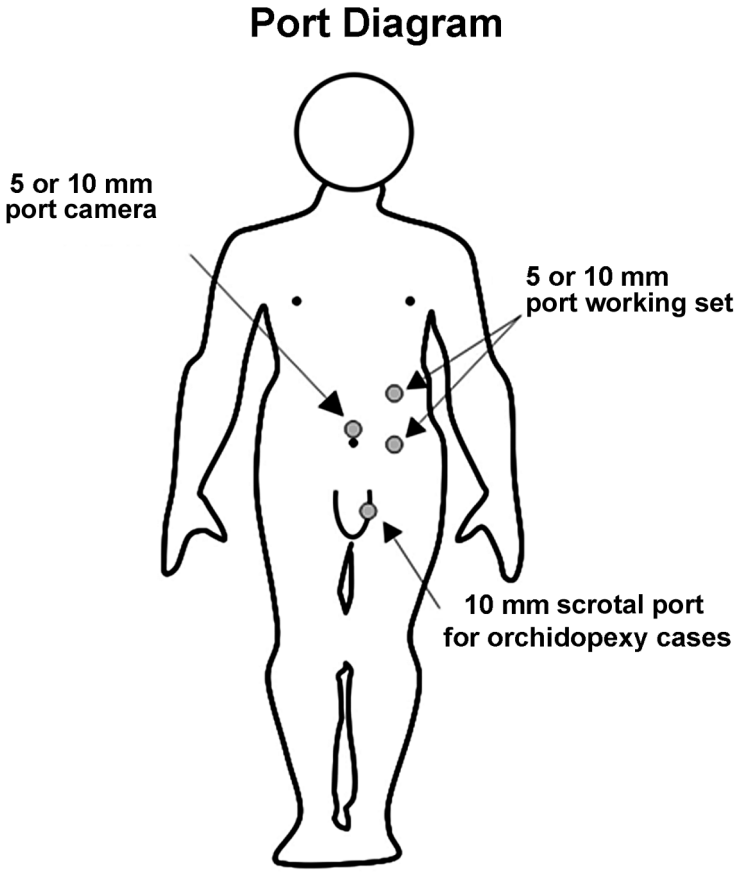

Figure 1 *– Surgery diagram for left laparoscopic approach. Note that port diameter varies according to patients' age.*

Table 2 *– Laparoscopic findings classification.*

Absent testis	Agenesis (absence of spermatic vessels and vas deferens). Vanishing testis (blind ending of spermatic vessels or vas)
Canalicular testis	Penetration of vas and spermatic vessels into the internal inguinal ring with or without directly seeing the testis
Abdominal testis	Localized between the inferior renal pole and the ipsilateral internal inguinal ring. Can be a normal or an atrophic gonad.
Peeping testis	Primarily in intra-abdominal position. The testis introduces itself into the inguinal canal due to the intra-abdominal pressure augmentation during the laparoscopic procedure. Usually associated with inguinal hernia and returns to its original position by pressing the inguinal region externally.

management was performed based on the laparoscopic findings (8,9). In cases of testicle absence , the procedure was interrupted, whereas in cases of intra-canalicular inguinal testis, open surgical exploration was performed. When intra-abdominal testes were found, immediate laparoscopic orchiectomy was performed for atrophic testicles, while patients with viable testicles underwent laparoscopic orchiopexy. The technique of this procedure has been previously described, stressing that in cases of low intra-abdominal testicle (located less than 2 cm from the internal inguinal ring) the procedure was straightforward, without transection of the spermatic vessels, while in those located higher (more than 2 cm from the internal inguinal ring) the vessels were sectioned to facilitate the appropriate descent of the testicle to the scrotum (6). When the vessels are transected, the testis is relocated into the scrotum either during the same surgical procedure (primary or one stage Fowler-Stephens) or the relocation is postponed for at least six months after vascular ligature (two stage Fowler-Stephens).

All the operated patients were followed-up for 6 to 100 months, and evaluated for the incidence of intra and post-operative complications, as well as for the final location and morphology of the operated testes. These complications were classified as normal (good size and consistence, in addition to appropriate position in the scrotum), atrophic (altered morphology, independent of the position) or malpositioned (normal morphology, but located above the scrotum). In cases of unilateral disease, the evaluation of cryptorchid testicle was based on the normal testicle. In cases of bilateral disease, this evaluation was based on clinical palpation as well as ultrasonography in some cases, comparing the obtained values with normal parameters in infancy and adulthood.

RESULTS

The initial laparoscopic findings are summarized in Table-3. One should note that five patients had bilateral disease, in which we had different diagnostic findings in each affected side as emphasized in Table-3.

Eighteen patients (20%) presented absent testicles, four due to agenesis and 14 to vanishing

Table 3 *– Laparoscopic results.*

	Number of Testes	
Diagnosis	**Unilateral**	**Bilateral**
Absence	18	8
Canalicular	17	15
Intra-abdominal	30	36
Sub total	65	59

Note: 5 patients had bilateral disease and with different diagnosis for each testis side (3 absent and 2 abdominal testicles)

testes. In these cases, the laparoscopic procedure was completed preventing the patients from any further unnecessary exploration. In 12 patients of this group, who were near pubertal age, a testicular prosthesis was inserted during the same surgical procedure.

Thirty-two patients (35.5%) had a diagnosis of intra-canalicular inguinal testicles. In this group, the difficulty in palpating the testis was due to regional obesity, the small size of the testis or general anesthesia, which facilitated the child's examination. The majority of patients underwent a conventional inguinal exploration, and those with viable gonads (34.4%) had an orchiopexy during the same procedure, while those with atrophic testicles (65.6%) underwent orchiectomy. Only one patient underwent a laparoscopic dissection of the inguinal testicle via the internal inguinal ring, where an atrophic testis was found, and removed. In this group, the older children also received testicular prosthesis at the same time. Interestingly, we observed that the presence of a hernia sac almost always indicates the presence of a canalicular testicle, particularly in peeping testis.

In 46 patients (51.1%), the testes were intra-abdominal, and treatment varied according to their morphology and position (Table-4). In three patients, four testicles were atrophic (one patient with bilateral disease). All were submitted to immediate laparoscopic orchiectomy. In the other 43 patients laparoscopic orchiopexy was performed. In 25 testicles of 19 patients, we performed the two stage laparoscopic Fowler-Stephens orchiopexy, with initial vascular transection. All were submitted to orchiopexy at least six months later. In 21 testicles of 15 patients, the orchiopexy was also done by laparoscopic technique, while the remaining four testicles were positioned by conventional inguinal approach.

The other 27 patients underwent primary laparoscopic orchiopexy, in a total of 29 testicles. In 3 of these testicles (3 patients), vascular ligature and section were necessary, while the majority (26 testicles) was relocated to the scrotum with preservation of the vascular pedicle.

Minimal follow-up period was approximately 6 months. Only 2 patients were lost to follow-up during a fifteen year protocol.

Of the 25 testicles advanced into the scrotum by the two step Fowler-Stephens technique, 18 (88%) presented good morphology and position in the scrotum, while 3 testicles became atrophic. Considering this same group, an 85% success rate was achieved with the laparoscopic second stage, as compared to a 100% success rate with the open approach.

Of the 25 testicles submitted to the primary laparoscopic orchiopexy, without vascular transection, 96% were considered successful, with good position and normal morphology, with only one testis developing atrophy. Among the testes submitted to primary orchiopexy with simultaneous vascular ligature, two presented atrophy, while one testis remained normal (success rate of 33%).

There was no intraoperative complication in our group of patients, and none required blood transfusion or conversion to open procedure. All patients who underwent a laparoscopic diagnostic procedure alone

Table 4 – *One stage vs. two stage Fowler-Stephens.*

Two stage surgery*	2nd Laparoscopic stage	Normal	18 (88%)
	21 testes	Atrophic	3 (12%)
	2nd Open stage	Normal	4 (100%)
	4 testes	Atrophic	0
One stage surgery**	With vascular ligature	Normal	1 (33%)
	3 testes	Atrophic	2 (67%)
	Without vascular ligature	Normal	25 (96%)
	26 testes	Atrophic	1 (4%)

** 19 patients; ** 27 patients.*

could be fed on the same day and were discharged the following day. Those who underwent orchiopexy were discharged on the second post-operative day. Post-operative pain was minimal and treated with common analgesics or non-steroidal anti-inflammatory drugs, according to patients' age.

In late follow up, we did not observe any post-operative complication in the abdominal or scrotal percutaneous ports, nor inguinal or incisional hernia.

COMMENTS

The treatment of non-descended testicles is mandatory due to the increased risk of infertility, present in up to 40% of the patients, as compared to 6% of control groups (10), including malignancy, which reaches 20 times that of normal adults (11).

Despite the recommendations for the treatment of the cryptorchid testis before 2 years of age, many of our patients were older, due to the socio-economic characteristics of the public health system in our country, the lack of parental information and difficult access to tertiary health care. Although fertility is already compromised in this age group, treatment is necessary not only for the risk of malignancy, but also for the satisfaction and improvement in the quality of the patient's life and parents´ concern for their children's health (12).

In relation to diagnosis, some tests can be used for appropriate therapeutic planning. In the case of bilateral impalpable testes, the stimulation with human chorionic gonadotrophin has only a relative usefulness, since a negative result, although suggestive of absent testes, cannot completely exclude the presence of a dysplasic gonad. Even in the case of a positive answer, it is not possible to establish the number, location and the laterality of the gonad (13). Despite a sensitivity of 70-90% in the diagnosis of inguinal testes, ultrasonography is not useful in intra-abdominal cases(14). Although presenting a better quality, both computed tomography and nuclear magnetic resonance lack sufficient sensitivity and specificity to be considered as gold standard diagnostic tools (15). More recently, the magnetic angioresonance was introduced with sensibility of 96% and specificity of 100%, but it is still a new method, with high costs, also requiring general anesthesia in children (16).

In relation to the treatment, the use of gonadotrophin for undescended testes presents a success rate of definitive descent to the scrotum of 21 to 56%, with better results in bilateral cases (13,14). Surgical treatment via an inguinal incision is the main treatment option for palpable testicles, but can also be employed for the evaluation and treatment of impalpable testis. In this situation, however, surgical exploration can often require large incisions and extensive dissections, especially in bilateral cases. This can be avoided using laparoscopic evaluation, with a sensitivity and specificity reaching more than 90% (17,18).

In 20% of our patients with testicular agenesis or vanishing testis, laparoscopic surgery was the decisive diagnostic method and saved these patients from any further incision or unnecessary investigation. In patients with intra-canalicular testicles, laparoscopy was fundamental for guiding the minimal inguinal exploration, which was augmented only in cases of a viable gonad, when orchiopexy was performed.

In cases of intra-abdominal testicles, the great advantage of laparoscopy is that, besides correct diagnosis, it enables the therapeutic handling of the testes at the same time. Additionally in cases of associated inguinal hernia (particularly in cases with peeping testis), the laparoscopic approach also enables the simultaneous treatment of the hernia sac with favorable results.

Careful dissection of the spermatic vessels as well as preservation of the peri-deferential vessels are fundamental to ensure testicular preservation. As regards late outcome, we have achieved results comparable to those reported in the literature for laparoscopic orchiopexy, with success rate of 88% for the staged Fowler-Stephens technique, and 96% in the primary orchiopexy without vascular transection (8,17,19). One should be aware of the inferior results of the laparoscopic primary orchiopexy with vascular ligature (primary or one stage Fowler-Stephens). In the literature (20), the reported success was 74.1%. In our series, with the exception of a few cases, we only reached 33% of well located and normal testes. Based on these results, the laparoscopic one stage Fowler-Stephens orchiopexy, with spermatic vessel ligature, has been abandoned in our Department.

Using laparoscopic procedures, the cosmetic aspect is remarkably more favorable as compared to open surgery , and the hospital stay and convalescence are much shorter. In the pediatric age group, these factors may not be so evident for the patient themselves, but certainly will be for the parents, who are able to resume their daily activities earlier. Furthermore, the laparoscopic orchiopexy presents excellent results in terms of diagnosis and therapy of the impalpable testis, which is why this technique has been routinely incorporated in our Department. It is noteworthy that our preference is the primary orchiopexy without transection of the gonadal vessels. However, in cases of very high testicles or those with short vessels we now recommend the two staged laparoscopic technique of Fowler-Stephens.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

Laparoscopy is an accepted diagnostic and treatment modality for non-palpable testes as performed in the current series. In this series, the percentage of intra-canalicular viable testis which was not palpable during the examination even under anesthesia is high (34.4% of 32 patients) and it is not similar to our experience (1). Whatever the reason, we encourage the authors to perform laparoscopic orchiopexy instead of converting the operation to open surgery in this situation.

Classification of intra-abdominal testes according to the measurement of distance between the testes and the internal inguinal ring is a good criterion but in our series, we have few cases, which do not match this criterion. Based on these observations, we prefer to examine the mobility of the testis by a laparoscopic forceps and to decide if the length of the spermatic vessels and ductus deferens is suitable for one or two stage operation.

In our series, a few cases were previously explored by open or laparoscopic technique at another center and, diagnosed as "absence of testis". In those cases, we had documented positive response to HCG stimulation test and diagnostic laparoscopy revealed the presence of an intra-abdominal testis. Therefore, we advocate performing an HCG stimulation test in patients with bilateral non-palpable testes before surgical exploration.

The authors performed testicular prosthesis placement following laparoscopic exploration in older patients with vanishing testis. We recommend a similar option for the younger patients and, this alternative approach could be offered to the parents before laparoscopic exploration. Inguinal exploration may be postponed and, testicular nubbins can be removed later at the time of testicular prosthesis implantation surgery if there is a consensus with the family (2).

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Self-Reported Urinary Continence Outcomes for Repeat Midurethral Synthetic Sling Placement

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ABSTRACT

Objective: To evaluate our experience with tension-free transvaginal tape (TVT) placement for the management of stress urinary incontinence (SUI) in women who had previously undergone a failed midurethral synthetic sling (MUS) procedure.

Materials and Methods: Ten women underwent retropubic TVT insertion for continued or recurrent SUI following a prior MUS procedure. No attempt was made to remove the previously placed sling at the time of surgery. A retrospective chart review was performed to obtain perioperative and follow-up patient information. Post-operatively, each patient completed a mailed incontinence questionnaire to assess self-reported urinary continence outcomes.

Results: All 10 women were available for follow-up at a mean period of 16 months (range 6 to 33). Four of the 10 patients achieved complete continence, and another three patients reported significantly improved continence and quality of life. Three women stated that their continence did not improve.

Conclusions: TVT placement may be a viable option for the management of women with persistent or recurrent SUI following an initial MUS procedure.

Key words: *female; urinary incontinence; stress urinary incontinence; prostheses and implants; slings*
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INTRODUCTION

Tension-free transvaginal tape (TVT) is one of the preferred therapeutic approaches for the treatment of female stress urinary incontinence (SUI). It is considered a minimally invasive yet effective surgical method for the management of SUI. Recently published TVT surgical results show a high success rate ranging from 80-95% with greater than five year follow-up (1-4). However, 5-20% of treated patients experience surgical failure with clinically significant recurrent or persistent SUI (1-3).

To date, no consensus exists for the management of SUI in women with a previous failed midurethral synthetic sling (MUS) procedure. Several possible treatment options have been described in the literature. These include pelvic floor rehabilitation, placement of an artificial urinary sphincter (5,6), periurethral injection of bulking agents (6), or most commonly a more invasive anti-incontinence surgery such as colposuspension or suburethral sling (6-8). Recently, some authors have advocated transvaginal shortening or tightening of the implanted tape for recurrent or persistent SUI after MUS (9-12). Another

option is to perform a repeat MUS. However, there is a paucity of published data on repeat MUS procedures for the management of persistent or recurrent SUI (10,13-16).

We describe our experience with retropubic TVT placement for the management of SUI in women with a previous failed MUS procedure. In this study we utilized a patient self-reported quality of life questionnaire to assess the efficacy of the procedure. To our knowledge, this is the first study to present data using a validated incontinence questionnaire to assess outcomes for TVT insertion following an unsuccessful MUS procedure.

MATERIALS AND METHODS

Following institutional review board approval, a retrospective chart review was performed to identify women that underwent placement of a TVT due to primary or recurrent failure of a MUS surgery for the management of SUI. A total of ten women (mean age 65 years, range 43 to 80) underwent retropubic TVT insertion at our institution between January 2004 and June 2006 following failure of a previously placed MUS. All procedures were performed by, or under the guidance of one experienced pelvic surgeon (A.R.S.). Preoperative evaluation included previous medical history, physical examination, urinalysis, urine culture, and video urodynamic evaluation. No patient had evidence of tape extrusion or erosion. Post-operatively, each participant received a telephone call from a non-biased third party informing them of the study prior to mailing of the International Consultation on Incontinence Questionnaire (ICIQ) (Appendix-1) (16). The questionnaires were accompanied by an informed consent as well as a brief outline describing the objective of the study. All ten patients completed and returned the consent and questionnaire forms. Complete continence was defined by a sum score of zero on the ICIQ. In other words, the patient was required to self-report total absence of urinary leakage to qualify as completely continent. We defined a score of 0 or 1, on a scale from 0 to 10, on question 3 of the ICIQ to indicate that urine leakage no longer impacted the patient's quality of life.

We have occasionally used periurethral bulking agents after TVT failure, however this paper focuses on those patients who underwent repeat TVT.

Retropubic midurethral synthetic sling placement was performed using the Gynecare (Ethicon, Somerville, NJ) TVT device. No attempt to locate or alter the previously placed sling was made at the time of surgery.

RESULTS

Placement of the TVT was performed in 10 patients following an initial unsuccessful MUS procedure (Table-1). The interval between the first MUS and second TVT procedure ranged from three to 32 months (average 14). All 10 women were available for follow-up at a mean period of 16 months (range 6 to 33). Five women underwent previous retropubic MUS, or TVT. The remaining five patients underwent a prior transobturator tape (TOT), including four using the in-to-out technique and one using the out-to-in method. Four patients underwent incision or removal of the initial MUS for voiding dysfunction. Three of these women had previously undergone TVT, the other underwent TOT, and required clean intermittent catheterization following the first procedure.

All ten patients demonstrated urodynamic evidence of SUI following original MUS placement prior to undergoing the second TVT procedure. The Valsalva leak point pressure was < 60 cm H_2O in three women. None had significant detrusor overactivity, although anticholinergics were used for subjective urgency. Physical examination confirmed the presence of genuine stress incontinence in all patients. All had some degree of urethral hypermobility.

At the time of TVT insertion, two women underwent concurrent procedures. One patient required anterior repair with porcine graft, while another underwent posterior repair. Both patients were discharged home on post-operative day one without a catheter in place. The eight patients who underwent TVT placement alone were all discharged home on the same day of surgery. Average blood loss and operative time for these eight patients was 10 mL (range 5 to 20) and 30 minutes (range 24 to 42), respectively. Including the two women who underwent additional surgery (one anterior repair, one posterior repair), the mean blood

Table 1 *– Patient information.*

N	Age (years)	Type of MUS 1st Surgery	1st Surgery Other Procedures	Time from 1st Surgery to MUS Incision (months)	Antichol	VLPP before 2nd Surgery (cm H_2O)	Type of 2nd MUS	Time from 1st to 2nd Surgery (months)	2nd Surgery Other	Post-op Antichol	Follow-up (months)
1	68	TOT	ant/post repair	N/A	yes	60-100	TVT	4	none	no	6
2	43	TOT	none	15	yes	> 100	TVT	18	none	yes	11
3	69	TVT	none	4	no	60-100	TVT	11	ant repair	no	11
4	70	TVT	post repair	1	no	> 100	TVT	17	none	no	18
5	80**	TVT	none	N/A	yes	< 60	TVT	32	none	yes	21
6	49	TOT	none	N/A	yes	< 60	TVT	3	none	no	22
7	70**	TOT	none	N/A	no	60-100	TVT	6	none	no	31
8	54	TVT	none	N/A	yes	> 100	TVT	14	post repair	no	33
9	79**	TOT	ant/post repair	N/A	yes	< 60	TVT	4	none	no	6
10	69	TVT	none	2	yes	60-100	TVT	29	none	yes	6

*TVT = tension-free vaginal tape/retropubic midurethral synthetic sling; TOT = transobturator tape; MUS = mid-urethral synthetic sling; ant = anterior; post = posterior; antichol = anticholinergic medication; N/A = not applicable; ** failed patients.*

loss and operative time for all ten patients was 22 mL and 50 minutes, respectively. No intraoperative or immediate postoperative complications occurred for any patients.

All 10 women completed the mailed ICIQ (Table-2). Four of the 10 (40%) patients achieved complete urinary continence indicated by a sum score of 0 for the ICIQ. Seven of the 10 women (70%) self reported a score of either 0 or 1 on question 3 of the ICIQ, thereby indicating that urine leakage no longer impacted their quality of life. Three patients were not significantly improved by their second procedure.

All three women that did not improve with TVT placement were immediate failures, exhibiting SUI following the initial procedure. Therefore, none of the three patients required incision or removal of the initial midurethral synthetic sling material.

Three of the ten patients use anticholinergics for overactive bladder-type symptoms. Each indicated on the incontinence questionnaire that urine leaks prior to getting to the toilet. However, all three women used anticholinergics prior to the TVT insertion, indicating that the second procedure did not result in de novo detrusor overactivity.

Only one patient had difficulty with bladder emptying after her second surgery. She underwent midurethral sling lysis following her initial TVT due to urinary retention. However, after initial TVT takedown her urinary incontinence was severe and adversely impacted her quality of life. The patient elected to undergo repeat TVT with the understanding that, as her preoperative urodynamics had suggested inefficient voiding, and may require CIC. Following the repeat TVT, the patient experienced no urinary

Table 2 – *ICIQ patient responses.*

Patient	Question		
	1	2	3
1	0	0	0
2	2	2	1
3	0	0	0
4	1	2	1
5	4	2	5
6	0	0	0
7	5	4	5
8	2	2	0
9	5	6	10
10	0	0	0

Questions:

1. *How often do you leak urine? (range, 0-5)*
2. *How much urine do you usually leak? (options: 0 none, 2 small amount, 4 moderate amount, 6 large amount)*
3. *Overall, how much does leaking urine interfere with your everyday life? (range, 0-10)*

leakage and indicated satisfaction with the outcome despite the need to perform CIC.

COMMENTS

Placement of a midurethral synthetic sling has become one of the preferred therapeutic modalities for the surgical management of female SUI. Despite reports of excellent outcomes with TVT placement, some women continue to experience persistent or develop recurrent SUI (1-3). The etiology of persistent or recurrent SUI following TVT is not well defined. Some theorize that the initial placement of the tape was too loose or positioned incorrectly, thereby preventing functional urethral kinking to occur during periods of increased abdominal pressure (17). Riachi et al. proposed that inappropriate intraoperative adjustment of the tape, failure of the tape to be fixed in place, or that the underlying pathology of the urinary incontinence mechanism was responsible for persistent SUI following TVT (13).

There are several surgical treatment choices for the management of SUI following a failed MUS procedure. Such options include placement of an artificial urinary sphincter (5,6), injection of periurethral bulking agents (6), or traditionally a more invasive anti-incontinence procedure such as colposuspension or placement of a suburethral sling (6-8). More recently some authors have advocated possible salvage options following a failed MUS procedure. These maneuvers include transvaginal shortening or readjustment of the implanted tape (9-12). Lo et al. presented, to our knowledge, the largest reported case series for treatment of recurrent SUI after a TVT procedure by shortening the pre-implanted tape under local anesthesia. Using this method they report a greater than 70% subjective and objective cure rate in 14 women (9). The main limitation of this technique, however, is the need to identify and dissect the tape free from adherent periurethral tissue. For example, Tsivian et al. reoperated on 12 women for SUI following failed MUS placement. During the surgery, the prior MUS could not be found in three women, and was embedded and unable to be dissected free in another (14). Similarly, Riachi et al. could not identify the previously placed tape in 1 of 2 women undergoing reoperation for recurrent SUI following an initial TVT procedure (13), and Villet et al. reported the failure to locate the previously placed synthetic sling in 1 of 3 women (10). If the tape was initially placed incorrectly, shortening would not improve the results. Therefore, despite the apparent efficacy of the transvaginal TVT tape shortening procedure for recurrent SUI, it requires the identification and subsequent periurethral dissection of the previously placed tape, which may prove to be difficult. We made no attempt to locate or alter the previously placed tape in our patients in order to minimize the periurethral dissection.

Another option for surgical management of a failed MUS procedure is to repeat the procedure, thereby eliminating any manipulation of the previously placed tape. Riachi et al. first described repeat application of a TVT in two patients at 8 and 9 months after the initial procedure. Both women were completely continent at 6 and 13 month follow-up (13). Villet et al. reported on two patients who underwent repeat TVT, no complications were reported and each woman was continent at four and 12 months of follow-up (10). In addition to these case reports, Tsivian et al. presented a case series of 12 women who underwent

repeat MUS for persistent or recurrent SUI following a previous MUS procedure. They report that 11 of 12 patients achieved full continence following repeat surgery. Interestingly, five patients underwent repeat TVT, four underwent intravaginal sling, and three underwent TOT placement. Unfortunately the authors did not utilize urodynamic evaluation nor present their telephone acquired questionnaire results for post-operative objective or subjective assessment (14). Recently, Moore et al. reported on the successful treatment of five women with recurrent SUI using a TVT following a failed prior TOT insertion (15).The largest series of repeat TVT has been reported by Lee et al. (16), who report similar results. They used both retropubic and transobturator approaches and noted significantly better cure rates with the retropubic approach.

In our series, 10 women underwent retropubic TVT for the management of SUI following a failed previous MUS procedure. Using the ICIQ, four women (40%) reported complete urinary continence, whereas another three women (30%) reported significant improvement in their quality of life. Three women did not improve following repeat TVT placement. The average age of these three women was 12 years greater than the four patients who became completely continent following repeat TVT, and two of the three women exhibited VLPP < 60 cm H_2O on preoperative video urodynamic evaluation. The results in this subset of patients are not surprising since patients with low VLPP have been shown to demonstrate lower cure rates following MUS procedures than patients with VLPP > 60 cm H_2O (18,19). Moreover, elderly patients have been shown to report decreased improvement following anti-incontinence procedures when compared to a younger cohort undergoing comparable surgeries (20).

Further analysis of the data showed no substantial difference in outcome between the five patients who underwent initial TOT in comparison to the five patients who had initial TVT placement. For those women with initial TOT placement, subsequent TVT resulted in two of the five becoming completely continent and three of the five indicating that urine leakage no longer impacted their quality of life. Similarly, for the patients who underwent TVT placement a second time, two became completely continent and four expressed that urine leakage no longer impacted their quality of life. The number of cases is too small to make definitive conclusions or meaningful statistical analysis.

All four of the patients who had undergone tape incision, did well, two were completely dry and two had minimal unbothersome leakage.

Advantages for performing TVT following a previously unsuccessful MUS include its minimally invasive nature, rapid patient recovery, and reported efficacy. As compared to transvaginal retensioning of the previously placed tape, repeat TVT insertion does not require identification of the initial sling material, thereby eliminating the need for any further periurethral dissection. In addition, our findings do not suggest any increased risk of surgical complications (difficulty with needle passage, bladder injury, erosion) when performing TVT placement after a prior unsuccessful MUS procedure. Although a questionnaire was not completed pre-operatively for comparison, the combination of urodynamically demonstrated SUI and the patient's desire to undergo repeat surgery indicates that urinary incontinence substantially impacted their quality of life at that time. A limitation of this study is the lack of objective data such as a pad test. However, we treat patients because they believe they have failed their prior management, not because we think they have failed. We therefore contend that patient-reported outcomes are the most important tool in which to assess the efficacy of this treatment.

CONCLUSIONS

We present a case series advocating application of the TVT for treatment of recurrent or persistent SUI following an unsuccessful prior MUS. Such an intervention could avoid the more extensive scarring, bleeding and perioperative complications associated with more invasive procedures and does not require additional periurethral dissection for identification of the previously placed material. Despite the short-term follow-up and small sample size, the results of our study suggest that TVT insertion may be a viable option for the management of failed previous MUS procedures. Further studies with longer follow-up and more patients are necessary to identify the best option for management of recurrent or persistent SUI following a previous MUS procedure.

CONFLICT OF INTEREST

None declared.

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Appendix-1

International Consultation on Incontinence Questionnaire (ICIQ)

1. How often do you leak urine? (Pick one box)

   0 □ Never
   1 □ About once a week or less often
   2 □ Two or three times a week
   3 □ About once a day
   4 □ Several time a day
   5 □ All the time

We would like to know how much you think leaks?

2. How much urine do you usually leak (whether you wear protection or not)? (Pick one box)

   0 □ None
   2 □ A small amount
   4 □ A moderate amount
   6 □ A large amount

3. Overall, how much does leaking urine interfere with your everyday life? (Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10
not at all a great deal

4. When does urine leak? (Please pick all that apply to you)

   □ Never – urine does not leak
   □ Leaks before you can get to the toilet
   □ Leaks when you cough or sneeze
   □ Leaks when you are asleep
   □ Leaks when you are physically active/exercising
   □ Leaks when you have finished urinating and are dressed
   □ Leaks for no obvious reason
   □ Leaks all the time

EDITORIAL COMMENT

With current understanding of pathophysiology of stress urinary incontinence (SUI), integral mid-urethra theory explains most of its occurrence and has enabled successful introduction of minimally invasive mid-urethral tension-free tapes with success rates over 80%. However, pathophysiology of the unfortunate 20% patients who failed the initial surgery needs attention. The factors for recurrence include, not exclusively, so-called intrinsic sphincter deficiency (ISD) of varied etiology, voiding dysfunction and overactive bladder, and have a great bearing on further management as well as counseling of these low-on-self esteem patients. This underscores the importance of detailed evaluation of these patients before planning surgical management.

The present study is a retrospective analysis of 10 cases with recurrent SUI following midurethral sling (TVT / TOT) and presents encouraging results of TVT in this subgroup. I would congratulate the authors for performing a detailed preoperative evaluation of all these patients including clinico-urodynamic evaluation, appropriate management of overactive bladder and adequate counseling (which led to a satisfied patient even on CIC). Management of recurrent SUI is not standardized and the authors are justified in their approach due to minimally invasive nature of the procedure. TVT has been reported as a viable treatment option for recurrent SUI after MUS as well as other surgical procedures.

Apart from the main conclusion, there are various 'hidden' important results in this article which need emphasis and are worthy of further investigations. ISD is a well known subgroup of SUI and is vaguely defined as severe incontinence, absence of urethral hypermobility (UH), open bladder neck (resulting from previous surgery, radiotherapy, old age, etc.), Valsalva leak point pressure < 60 cm H_2O and maximal urethral closure pressure < 20 cm H_2O. There are several reports to suggest lower, though clinically significant, success rates of MUS (especially TOT) in these patients more so in absence of UH. In the present study, two of three women who failed the repeat procedure had a Valsalva leak point pressure < 60 cm H_2O; it would be interesting to know degree of hypermobility and preoperative degree of incontinence in these patients. Although far from standard, it seems plausible to opt for some alternative form of treatment, e.g. injection therapy or compressive slings at bladder neck level in case of more than one 'risk factors' of ISD, especially absence of UH.

Voiding dysfunction (VD) has been reported to be more common after TVT than TOT, though the data on latter is limited. Four of the 10 analyzed patients had had release of tape for voiding dysfunction leading to recurrent SUI; interestingly 3 of these had undergone TVT, and one TOT. It would be desirable to report the incidence of VD after each procedure in their experience. Furthermore, pre-existing voiding dysfunction and urethral relaxation voiding patterns (with detrusor pressure < 12 cm H_2O) have been reported to be risk-factors for postoperative urinary retention and need for release of sling after TVT. Therefore, it would be worthwhile to report voiding function and voiding mechanism in these women.

I believe we have reached a stage where our focus should shift to standardizing the management of recurrent SUI. A practical approach to produce preliminary guidelines would be to perform some sort of meta-analysis of the existing case series and then to formulate plans of prospective randomized trials comparing various strategies.

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EDITORIAL COMMENT

The authors present their experience with redo tension -free transvaginal tape placement for the management failed midurethral sling (MUS). MUS procedure has gained wide acceptance for the treatment of female urinary stress incontinence. However, failure rate ranges between 5 to 20 % (ref .3,4 of the reviewed manuscript) and with the widespread use of this technique, the practicing surgeon will encounter a considerable number of failures.

What should be the optimal management of MUS failure? There is scarce data in the literature, therefore, in spite of the small series and short-term follow up, lack of objective data (physical exam, stress test, pad test etc) presented herein, this manuscript offers well-timed and important contribution in data accumulation and improvement of our understanding in resolving this problem.

One should note, that the preoperative work-up of MUS failure should include cystoscopy to exclude tape erosion into the bladder or/and urethra, especially in patients with irritative voiding symptoms.

Additional, well designed comparative studies are warranted to answer questions such as optimal timing of the salvage procedure, and whether repeat MUS should be applied or different approach is appropriate, and if MUS is chosen what is the preferred route, -transobturator or retropubic?

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Histopathological Evaluation of Urethroplasty with Dorsal Buccal Mucosa: An Experimental Study in Rabbits

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ABSTRACT

Purpose: Buccal mucosa is a widely accepted tissue for urethroplasty. The exact healing and tissue integration process, mainly the histological characteristics of dorsal buccal mucosa graft urethroplasty when used dorsally to reconstruct the urethral plate has not previously been assessed, and thus we developed an experimental model to address this question.
Materials and Methods: In 12 New Zealand rabbits (weight 2.5 kg) we surgically created a dorsal penile urethral defect. A buccal mucosa graft was sutured to the corpora and tunica albuginea, and the ventral urethra anastomosed to this new urethral plate. The animals were divided in three groups and sacrificed 1, 3 and 6 weeks after surgery (groups 1, 2 and 3). A retrograde urethrogram was obtained at autopsy in the last group and the penis analyzed histologically with hematoxylin-eosin and Masson's staining.
Results: The urethrograms showed no evidence of fistula or stricture. In group 1 the histopathological analysis showed submucosal lymph-mononuclear inflammatory edema, numerous eosinophils and squamous epithelium integrated into the adjacent urothelium. In group 2 there was no evidence of an inflammatory response but rather complete subepithelial hyaline healing, which was more marked in group 3.
Conclusion: Healing of buccal mucosa grafts to reconstruct the urethral plate can be achieved by total integration of the squamous epithelium with the urothelium, maintaining the original histological properties of the graft with no fibrosis or retraction.

Key words: *urethra; buccal mucosa; rabbits; experimental; surgery*
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INTRODUCTION

Urethral reconstruction under several pathologic conditions, such as strictures, traumatic defects, epispadias, and mainly in hypospadias, is one of the oldest problems in reconstructive surgery and one of the greatest surgical challenges for the surgeon. A variety of donor tissues have been used both experimentally and clinically for urethral repair, including free penile or preputial graft (1), hairless-skin grafts (2), bladder mucosal graft (3), buccal mucosal graft (4), tunica vaginalis graft (5), peritoneal graft (6), intestinal submucosal graft (7) and more recently the tongue (8). Some of these methods have met with limited success and subsequently were abandoned.

Buccal mucosa grafting for urethroplasty of both urethral stricture and hypospadias repair has gained widespread acceptance during the past 10 years. With the initial description by Humby dating back to 1941, the method was reintroduced into the urologic literature in 1992 by Mainz et al. (4). Reported clinical results in literature have been extremely

favorable both using the buccal mucosa as the ventral or dorsal component of the neourethra (9,10).

Despite wide clinical use, little is known about the underlying mechanisms that incorporate the buccal mucosa graft into the urethral defect. A thorough understanding of this process could improve clinical outcome, which was achieved after defining the mechanisms of buccal mucosa grafting.

The aim of the present study was to investigate how healing progresses after dorsal buccal mucosa graft urethroplasty in a rabbit model, and the histopathological outcome of the procedure.

MATERIAL AND METHODS

Twelve New Zealand White rabbits aged approximately 6 weeks and weighing 2.0 to 2.5 Kg were acclimated in the Experimental Research Animal Surgery Department for one week before the study. The experimental protocol was reviewed and approved by the Local Animal Research Committee (approval nº 1047/03).

The rabbits were anesthetized with intramuscular ketamine hydrochloride (30 mg/Kg) and intramuscular xylazine (5 mg/Kg) and received a preoperative dose of gentamicin (1 mg/Kg). After an adequate level of anesthesia was achieved, the penis was anesthetized with xylocaine and a 6F urethral catheter was inserted. Under sterile conditions, the penis was released by dividing the perineal skin web between the ventral aspect of the penis and the anus. Each urethra was surgically exposed and operated under optical magnification (surgical microscope - 10x).

The urethra was carefully dissected and mobilized off the tunica albuginea. After exposing the urethra, a dorsal segment measuring 1.0 x 1.0 cm was excised in all rabbits (urethral defect). A buccal mucosal graft was harvested from the cheek and tailored according to the area of the removed tissues. The graft was obtained by sharp dissection with fine scissors. The dissection was facilitated by prior submucosal injection of saline solution. The resulting wound was left open after careful coagulation of bleeding vessels.

The buccal mucosa graft was placed dorsally over the corpora cavernosa and tied with six interrupted polygalactin (Vicryl) 7-0 sutures. The mucosal margin of the urethral defect was sutured to the graft using 7-0 Vicryl sutures in a continuous fashion. The mucosal surface of the graft was always placed as the lumen of the reconstructed urethra. The skin was closed with a running 4-0 Vicryl stitch. Neither stent nor dressing was used. The operative technique is outlined in Figure-1.

The animals were recovered and returned to our chronic care facility. The animals were examined daily to monitor wound healing.

The experimental animals were divided into three equal groups and were sacrificed at 7 days, 3 weeks and 6 weeks after surgery, respectively. A retrograde urethrogram was taken at autopsy in the last group.

At the scheduled sampling time the animals were sacrificed with an overdose of Ketamine injection. The entire penis was examined and removed. The penises were fixed in 10% formaldehyde and transverse sections cut to produce segments of 5 mm each, processed into paraffin blocks, and serially sectioned and stained with hematoxylin-eosin and Masson's trichrome. An experienced pathologist (RD) examined the specimens and evaluated the severity of acute and chronic inflammation, foreign body reaction, and scar formation. Masson's trichrome stain was used to localize collagen. With Masson's trichrome stain, the nuclei stained from deep mauve to black, cytoplasmic elements red and blue, muscle red and collagen-mucus green.

RESULTS

There were no deaths related to the procedure and all animals survived their intended survival period without evidence of infection, voiding difficulties, or fistula formation.

There were no difficulties associated with buccal mucosa harvesting and the macroscopic appearance of the operated penises was normal.

One week after surgery the buccal mucosa graft area had a proliferation reaction in all rabbits. There was no significant necrosis or erosion of any graft. A moderate infiltration of polymorphonuclear cells was observed, representing an acute inflammatory reaction (Figure-2).

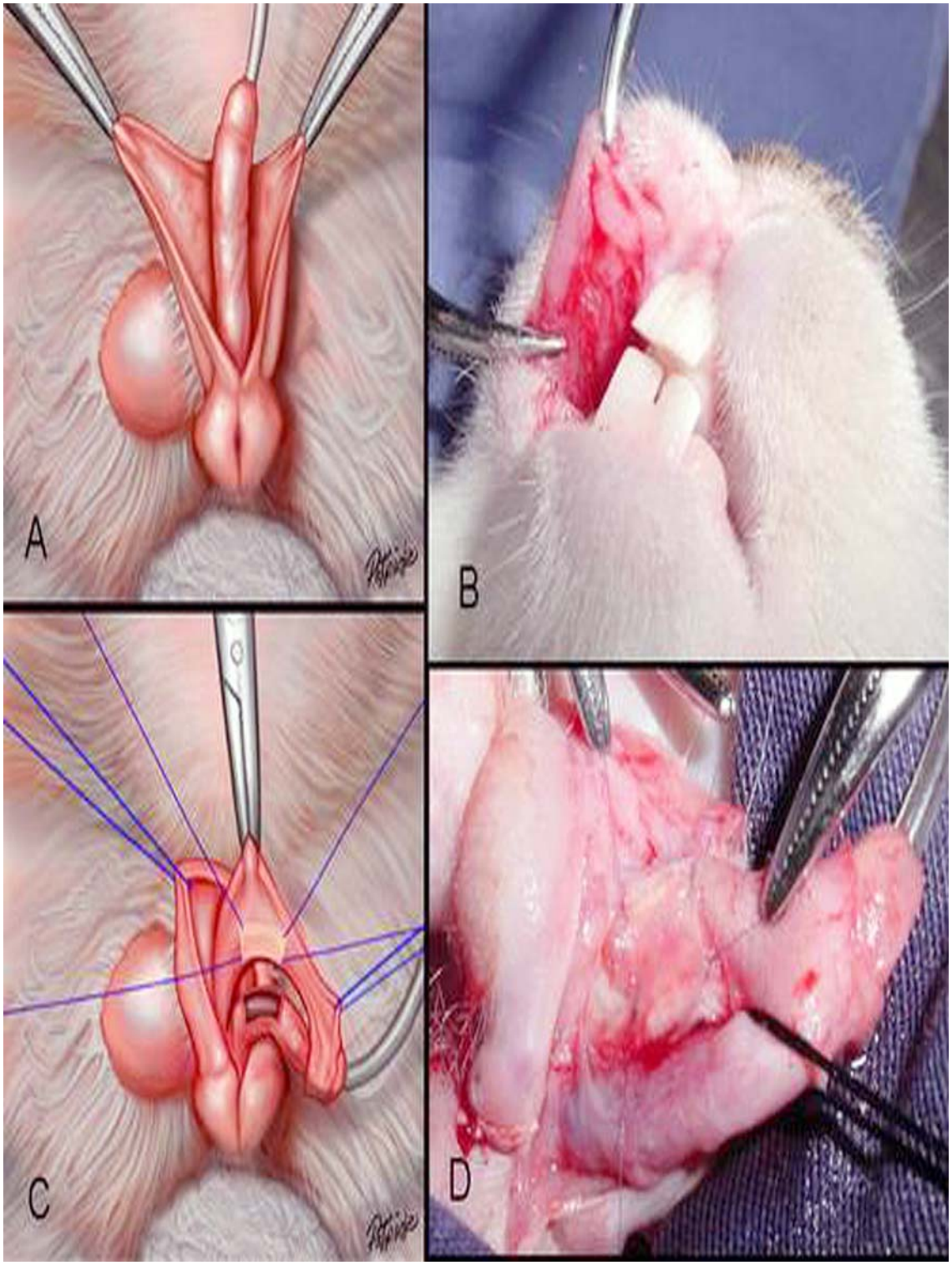

Figure 1 – *Operative technique. A) The penis is degloved and the urethra is dissected and mobilized. B) Buccal mucosa graft was harvested from the cheek. C) and D) The buccal mucosa graft was placed dorsally over the corpora cavernosa and tied with six interrupted polygalactin (Vicryl) 7-0 sutures.*

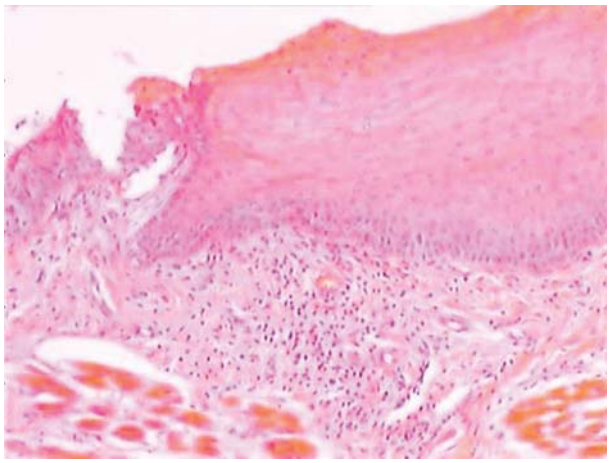

Figure 2 *– The buccal mucosa graft one week after surgery. A moderate infiltration of polymorphonuclear cells was observed.*

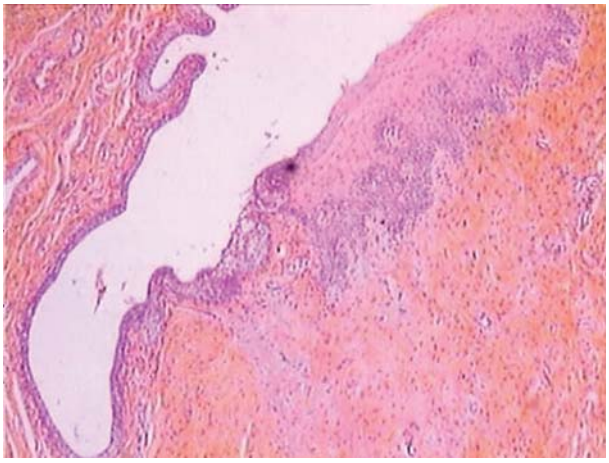

Figure 3 *– The buccal mucosa graft three weeks after surgery. Extensive neovascularization was evident in the subepithelial layer with a streaming of fibroblasts toward the graft.*

Three weeks after surgery extensive neovascularity was evident in the subepithelial layer with a streaming of fibroblasts toward the graft (Figure-3). Complete disappearance of the polymorphonuclear cells, representing resolution of the inflammatory reaction was evident by 6 weeks postoperatively. The histological appearance of the graft at postoperative week 6 is shown in Figure-4.

The typical squamous epithelium of buccal mucosa and minimal inflammatory cell infiltration in the subepithelial tissues were observed in all rabbits

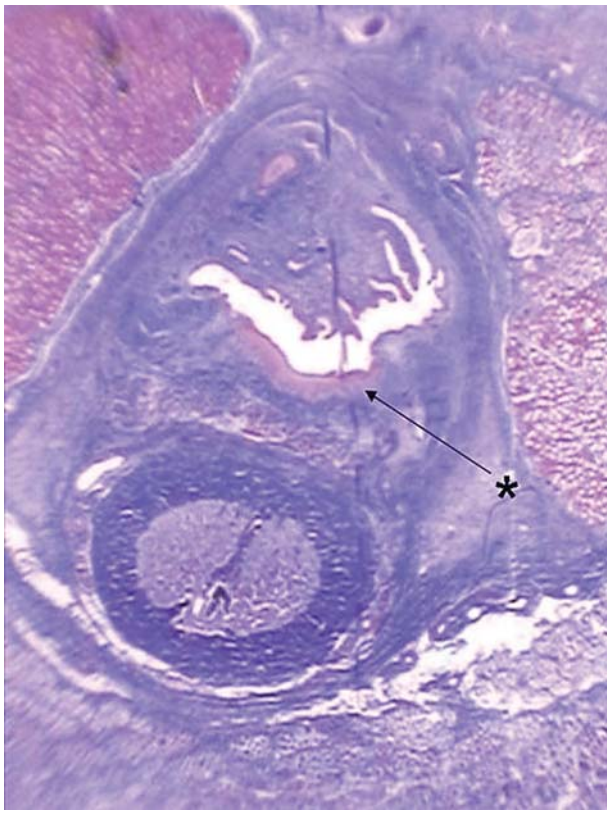

Figure 4 *– The histological appearance of the graft at postoperative week six.*

at the grafted buccal mucosa six weeks after surgery. Minimal fibrosis was observed. Microscopically the junction of the graft and normal urethra was identifiable in all groups. Six weeks after surgery retrograde urethrograms confirmed the maintenance of a wide urethral caliber without any signs of stricture or extravasation (Figure-5).

COMMENTS

The choice of the substitute material for urethroplasty during hypospadias repair is the most important factor in determining the resulting complication rate for each surgical technique in urethral reconstruction; thus, a controversial debate is ongoing about the ideal material, especially in the repair of complex hypospadias.

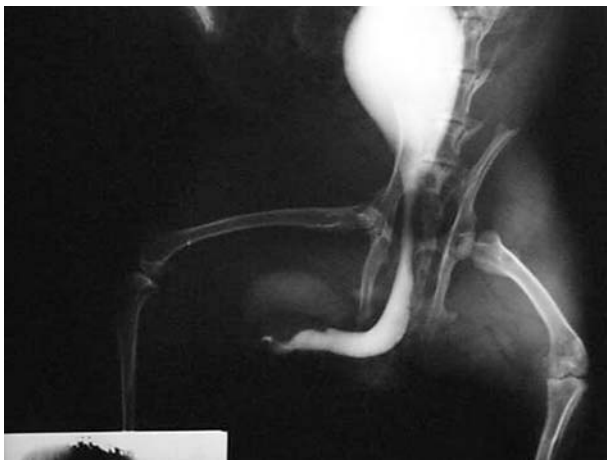

Figure 5 – *Retrograde urethrogram six weeks after surgery confirmed the maintenance of a wide urethral caliber without any signs of stricture or extravasation.*

Currently, buccal mucosa has become increasingly popular among pediatric urologists for urethral replacement during complex hypospadias repairs when local epithelial tissue is unavailable. Initial reports by Duckett et al.(11), Baskin and Duckett (12), and Burger et al. (4) have reported series with relatively low complication rates. Buccal mucosa seems to have distinct advantages over other materials due to its high degree of histological similarity to the normal urethra as revealed by morphology studies (13).

In contrast to bladder mucosa and penile skin, buccal mucosa comprises a thin submucosal and a thick epithelial layer. Whereas the thin submucosa may be important for fast and easy revascularization, stability of the material seems to be provided by the thick epithelial layer.

Additional immunohistochemistry studies have revealed a similar cytokeratin pattern between buccal mucosa and normal urethra as well as a parallel amount of immunoglobulin A in both tissues (13).

Although buccal mucosa grafts are performed for the surgical reconstruction of urethral problems, little is known about the mechanism by which engraftment occurs.

In the current study we developed a rabbit model to study the temporal healing process after a buccal mucosa dorsal graft urethroplasty. This rabbit model was used by our group in previous urethral reconstructive studies with success (14). In this model we used the tunica vaginalis graft placed dorsally anchored directly to the corpora as proposed by Barbagli et al.(15).

Barbagli et al. (15) argue that the dorsal location represents the best blood supply for graft take, prevents diverticulum formation, and is technically easier than a flap procedure. They also suggest that ventral placement of the graft leads to diverticulum formation and may impair the spongiosal blood supply.

In 2002, El-Sherbiny et al. (16) used an animal model of adult male mongrel dogs to compare the functional and pathological characteristics of three types of graft materials (buccal mucosa, bladder mucosa and free full-thickness skin) for urethroplasty. Buccal mucosa grafts were associated with the lowest rate of complications (12%), followed by bladder mucosa (37%) and free skin grafts (62%). Filipas et al. (13) reported the result of histological and immunohistochemical pattern of full-skin and buccal mucosa grafts after exposure to urine in a pig model and indicated that the buccal mucosal graft showed significantly fewer adverse histopathological findings after long-term exposure to urine than the full-skin graft and is therefore a preferable material for urethral reconstruction.

It is widely accepted based on experimental experience that the thickness of the lamina propria, and especially the degree of native vascularity of the donor and recipient sites, influence the chances of graft take. Nevertheless, the viability of a graft depends on the neovascularization. In our study the buccal mucosa showed great formation of neovascularity three weeks after surgery.

To our knowledge the present experimental study is the first to describe the histological end aspect of the healing process of the buccal mucosa urethroplasty. We did not intend to define which physiological parameters or cytokeratins were involved but primarily to understand whether the buccal mucosa maintains its histological characteristics or undergoes metaplasia. In this study animals were sacrificed at 1, 3 and 6 weeks postoperative, because this interval was considered to provide sufficient time for wound healing.

The experimental study here presented reinforces the role of dorsal buccal mucosa as an excellent tissue source for urethral reconstruction. Despite widespread use in urethral stricture, it has only recently been incorporated to hypospadias repair in a two-step approach basis (17,18). Snodgrass et al. (18) reported outcomes from staged buccal graft urethroplasty after failed hypospadias surgery. In this study 25 patients underwent stage 1 repair following an average of 4.4 prior hypospadias surgeries and 20 patients underwent stage 2. There were no cases of meatal stenosis, neourethral stricture or diverticulum. The authors concluded that staged buccal graft reoperation reliably creates a well vascularized substitute urethral plate for tubularization with low complication rates and good cosmetic outcomes.

We have used the dorsal buccal mucosal graft as a way to reconstruct the urethral plate after urethral plate section to straighten the penis in complex primary hypospadia forms (19). This step restores the continuity of the urethral plate and allows the use of a preputial flap that can be anchored onlay to the buccal mucosa concomitantly. We have previously presented the technique and the outcome of initial results and outcome has proved to be very favorable (19).

The patency of the urethra in radiological studies and the fine histopathological integration of dorsal buccal mucosa to the native urethral mucosa as shown here in a single procedure, support our concept of dorsal grafting plus onlay ventral flap as a useful and viable strategy for one-step urethral reconstruction in almost every complex primary hypospadia patient.

Interestingly the same study performed using the tunica vaginalis as the dorsal part of the urethra showed that this tissue, being different from the buccal mucosa, changes its histological properties and resembles the urethral epithelium (14). Nevertheless, the concept of dorsal grafting plus onlay flap in urethroplasty seems to function independently from the dorsal component (buccal mucosa or tunica vaginalis). We stress that the availability of long term follow-up studies using buccal mucosa in urethral reconstruction justifies our present preference for its use as first choice tissue in hypospadia repair (the three-in-one technique). We hypothesized that tunica vaginalis could have the same place as an alternative source of tissue for dorsal graft urethroplasty. However, further clinical series with long term follow-up would be required to confirm this theory. The authors also agree that "the three-in-one concept" in the clinical setting deserves long term approval although it could be regarded as a valuable option.

We also accept that the results found in the present study performed in an untouched urethra may vary when treating a recurrent failed urethral repair and only a specific study under similar conditions could provide a definite conclusion regarding urethral substitution surgery.

CONCLUSION

A urethroplasty with dorsal buccal mucosa in rabbits showed total integration to the adjacent epithelium, maintaining their histological characteristics, without occurrence of fibrosis, retraction or necrosis.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

After the original publication by Orandi in June 1968 at the 24th Annual Meeting of the British Association of Urological Surgeons in Cardiff (1), the one-stage flap urethroplasty, based on Orandi's original suggestions, was popularized by Quartey, McAninch and Jordan (2-4). In 1994, Snodgrass, was the first to describe the tabularized, incised plate urethroplasty for distal hypospadias repair (5). After 5 years due to the description of these techniques, Hayes and Malone suggested laying an oral mucosal graft into Snodgrass' midline incision of the urethral plate in patients with failed hypospadias repair (6). In this past decade, the interest in buccal mucosa as a substitute material in the reconstruction of the penile

urethra has been attracting the attention of most of reconstructive surgeons. Recently, Barbagli et al. provided a retrospective evaluation of the outcome in patients who underwent one-stage penile flap or graft urethroplasty (7). These authors found that the use of grafts for one-stage penile urethroplasty showed a higher success rate (80.0%) compared to flaps (66.7%). The difference in the success rate between oral mucosal grafts and skin grafts was not clinically significant.

Souza and co-workers should be praised for their study as it introduces readers to an aspect of "urethral basic science" and provides some answers to the knowledge gap. They performed a histopathological assessment of the exact healing process of buccal mucosa graft, when it was used dorsally to reconstruct the urethral plate in vivo animal model of penile stricture. After surgically creating a dorsal penile urethral defect, a buccal mucosa graft was sutured to the corpora and tunica albuginea. Animals were stratified into three different groups according to timing of histopathological analysis. After one week histopathological analysis showed submucosal lymph-mononuclear inflammatory edema, numerous eosinophils and squamous epithelium integrated into the adjacent urothelium (Group-1). After 3 weeks there was no evidence of an inflammatory response but complete subepithelial hyaline healing (Group-2), which was more marked after 6 weeks (Group-3). The authors concluded that the healing process of buccal mucosa grafts, used for reconstructing the urethral plate is by total integration of the squamous epithelium with the urothelium, maintaining the original histological properties of the graft with no fibrosis or retraction.

Currently, oral mucosa seems to be unsurpassed as donor substitute material in adult anterior urethroplasty, however pediatric and general urologists who are involved in the reconstruction of urethra are facing new challenges. What is the ideal harvest site? The most common harvest sites for oral mucosa are the lower lip and the cheeks. Simonato et al. and Barbagli et al. recently reported the tongue as an alternative donor site in graft urethroplasty (8,9). Furthermore what could be the role of tissue engineering? All these issues will be addressed in the near future.

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EDITORIAL COMMENT

For hypospadias repair more than 300 techniques and their modification have already been published (1). Buccal mucosa can be used in primary reconstruction, as well as after failed reconstruction if no other material is available. Initial animal experience in dogs demonstrated that this technique is feasible. Buccal mucosa has been used at our institution for urethral reconstruction since 1990 (2). Placing the Buccal mucosa graft on the dorsal site was popularized by Barbagli et al. in 1998 (3).

Souza and colleagues from Brazil investigated the use of buccal mucosa in a rabbit model as a dorsal onlay in primary hypospadias repair. They divided the 12 rabbits into 3 groups according to scarification time for histopathological investigation. They observed acute inflammatory reaction after 7 days, a good neo-vascularization after three weeks and some resolution of the inflammatory reaction with minimal fibrosis after 6 weeks.

Although each group consists of only a few animals (n = 4) and the results are confined to a description of the histopathological findings with no quantification, this study demonstrates that buccal mucosa causes no severe reaction if used for urethral reconstruction.

However, this experiment has its limitations. The authors used buccal mucosa in healthy tissue, and the animals had no previous surgery. It would be interesting to see what would happen if buccal mucosa was used for secondary reconstruction. The authors completed their experiment after 6 weeks. It would have been of some interest to see what would happen in the long run. Is there more fibrosis? Does the urothelium replace the buccal mucosa? Does the buccal mucosa undergo changes? These questions should be addressed in further long-term studies. This study is one of the first to investigate histopathological findings after urethral repair using buccal mucosa. More studies should be performed, in particular from the aspect of tissue engineering using buccal mucosa.

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EDITORIAL COMMENT

We congratulate the authors, which developed an elegant experimental model in the rabbit in order to evaluate the healing progress and the histopathological outcome of the dorsal buccal mucosa graft urethroplasty. The results of the study indicate that the buccal mucosa shows total integration to the adjacent epithelium, maintaining the histological characteristics without occurrence of fibrosis, retraction or necrosis.

In February 2006 we described the results of a pilot study on the use of the tongue (lingual mucosa graft - LMG) as an alternative donor site for graft urethroplasty with good functional and aesthetic results (1). We performed a urethral biopsy of LMG after 3 months which revealed absent pathological alterations in the nonkeratinizing, stratified lingual epithelium (1).

After this preliminary experience, our group (2) and other authors (3,4) confirmed that LMG is an excellent graft material with the advantage of potential minor donor site complications. A specific study on the donor site morbidity associated to a LMG provided further evidence that LMG may be harvested with only temporary donor site discomfort and without long term complications, confirming that the tolerability of the harvesting procedure is very high with minor risks of donor site complications (5). Minor donor site morbidity was also obtained by otorhinolaryngologists (6), which had an awaked interest in using LMG after our pilot study (1) to reconstruct and restore epithelial continuity of buccal/lip mucosal defects after tumour resection.

It would be very interesting if the authors could apply their experimental rabbit model, if technically possible, to evaluate if total integration to the adjacent epithelium with maintenance of the histological characteristics occur when a LMG is used for urethroplasty. In this way we may have a comparison of the lingual and buccal mucosa grafts.

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Zoledronic Acid Effects Interleukin-6 Expression in Hormone-Independent Prostate Cancer Cell Lines

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ABSTRACT

Objective: To investigate the inhibitory effects of zoledronic acid (ZA) on tumor related growth factor IL-6 in hormone resistant prostate cancer cell lines. The association between apoptosis and IL-6 inhibition was also assessed.
Materials and Methods: PC-3 and DU145 cell lines were treated with different concentrations of ZA (1-100μM) at various intervals (24-72 h.). The cell viability was investigated by XTT assay and apoptotic effect was evaluated by cell death detection ELISA kit. Caspase 3/7 activity assay was performed to confirm apoptosis. IL-6 levels were measured by ELISA in the supernatant, and these data were also confirmed by IL-6 mRNA analysis using RT-PCR.
Results: PC-3 and DU145 cell lines were sensitive to ZA mediated cytotoxicity in a dose- and time-dependent manner. However, the apoptotic effect was significantly different among PC-3 and DU145 cells ($p < 0.05$). IL-6 secretion was significantly lower in both cell lines, compared to the untreated control cells ($p < 0.05$). Although the increased inhibition of IL-6 secretion was associated with increased apoptosis in DU145 cells ($p = 0.002$), there was no similar association for PC-3 cell line ($p = 0.347$). When compared to the untreated controls, the number of cDNA copies was significantly lower in the ZA treated DU145 cell line at doses of 30 and 90μM ($p < 0.05$), suggesting a reduced expression of IL-6 mRNA.
Conclusion: ZA exhibited a time- and dose-dependent apoptotic effect on PC-3 and DU145 prostate cancer cell lines and this effect was associated with inhibited secretion of IL-6 in DU145 cell line.

Key words: *prostate cancer; zoledronic acid; interleukin-6; experimental*
Int Braz J Urol. 2008; 34: 355-64

INTRODUCTION

Prostate cancer is most common among elderly men, and in 2007, the estimated number of the newly diagnosed prostate cancer cases was 218.890 in USA (1). Although local curative treatment strategies are the most appropriate procedures in organ-confined disease, androgen deprivation therapy represents the standard treatment in patients with metastatic prostate cancer. Nevertheless, the development of hormone resistant prostate cancer and progression is inevitable during androgen deprivation treatment. Unfortunately, no any other effective and curative alternative treatment has been reported for these patients.

The new treatment modalities are primarily focused on growth factors that stimulate the proliferation of prostate cancer cells. Interleukin-6 (IL-6) is a growth factor for prostate cancer cells and its high serum levels are known to be directly associated with clinical prognosis of the disease (2,3). It has also been shown that IL-6 signaling pathway is active and up-regulated in organ-confined prostate tumors (4) and

IL-6 signaling pathway is actively used in metastatic prostate cancers and hormone independent prostate cancer cell lines.

Several clinical trials have already demonstrated the beneficial effects of bisphosphonates in prostate cancer patients (5,6). The growth of metastases may be inhibited by modifying the bone microenvironment using bisphosphonates. They also exert direct cytotoxic and apoptotic effects on a variety of human tumor cell lines including myeloma, breast cancer and prostate cancer (7-9).

Zoledronic acid (ZA) is the most potent nitrogen containing bisphosphonate compound. It has been shown to inhibit cell growth and induce apoptosis in prostate cancer cell lines DU145, PC-3 and LNCaP (10). Current evidence on the effects of ZA suggests that it is a potential chemotherapeutic agent for the treatment of prostate cancer, either as monotherapy or in combination. Despite the overwhelming in vitro studies investigating the anti-tumor activity of the combined use of ZA with different chemotherapeutics, the molecular targets and mechanisms of ZA in tumor cells remains a subject of debate.

We hypothesize that ZA may exert its anti-tumor effect by inhibiting the tumor related growth factor IL-6. Considering the potential role of IL-6 in the growth regulation of PC-3 and DU145 cell lines, the present study was planned to investigate the relationship between the anti-tumor activity of ZA and IL-6 secretion in these cells under in vitro conditions.

MATERIALS AND METHODS

Chemicals - Cell culture supplies were obtained from Biological Industries (Kibbutz Beit Haemek, Israel). Zoledronic acid was a generous gift from Novartis Pharmaceuticals Inc. (Basel, Switzerland). The stock solution of zoledronic acid was prepared at a concentration of 1 mM in distilled water and aliquots were stored at -20°C. All other chemicals, unless otherwise mentioned, were purchased from Sigma Chemical Co (USA).

Cell lines and culture - The androgen-refractory prostate cancer cell lines, PC-3 and DU145, were preferentially used since they secrete IL-6 and actively use IL-6 signaling pathway for growth promoting effects (11) and to maintain resistance to chemotherapy. These cell lines were kindly provided by Dr. Levent Turkeri from Marmara University, Istanbul, Turkey. PC-3 and DU145, adherent cell lines were cultured in RPMI 1640, supplemented with 10% heat-inactivated fetal bovine serum, 1% L-glutamine and 1% penicillin-streptomycin. All cell cultures were incubated at 37°C in 5% CO_2 and 95% air.

Cell viability assay - The effects of different concentrations of zoledronic acid (1,10,30,60,90, and 100µM) on PC-3 and DU145 cell lines were evaluated by using XTT cell proliferation kit (Roche Applied Science, Mannheim, Germany). Following the verification of cell viability by tryptan blue exclusion test, cells were plated on a 96-well plate in 200µL culture medium at a concentration of 10^4 cells/well. At 24, 48 and 72 hours of incubation, a 50µL of XTT labeling mixture was added to each well. The optical density was measured at 450 nm with a reference wavelength at 650 nm using a microplate reader (Beckman Coulter, DTX 880 Multimode Reader). The percentage of cytotoxicity was calculated as follows:

$$\% \text{ Cystotoxicity} = 1 - \frac{\text{A of experimental well}}{\text{A of positive control well}} \times 100$$

where A is the absorbance.

Evaluation of apoptosis - The Cell Death Detection ELISA kit (Roche Applied Science, Mannheim, Germany) was used to detect mono-oligonucleosomes (histone-associated DNA fragments) as an indicator of apoptosis after zoledronic acid induced cell death. Briefly, cytoplasmic lysates from untreated controls and zoledronic acid treated cells were transferred to a streptavidin-coated plate supplied by the manufacturer. A mixture of Anti-histone-biotine and Anti-DNA-POD were added to cell lysates and incubated for 2 hours. The complex was then simultaneously conjugated to form an immune complex on the plate, which then was read for optical density at 405 nm with a reference wavelength at 490 nm. The enrichment of mono-oligonucleosomes in cell lysates was calculated as absorbance of zoledronic acid treated cells/absorbance of untreated controls.

Caspase 3/7 activity assay - The Caspase-Glo 3/7 assay (Promega, Madison, WI) was used to measure caspase 3/7 activity, according to the manufacturer's instructions. PC-3 cells were plated on a 96-well plate in 100µL culture medium at a concentration of 10^4 cells/well. After incubation with increasing concentrations of zoledronic acid, 100µL of Caspase-Glo 3/7 reagent was added to each well. Then the mixture was incubated for one hour at room temperature and the luminescence of each sample was measured using a plate-reading luminometer (Beckman Coulter, DTX 880 Multimode Reader).

Determination of interleukin-6 secretion - IL-6 levels were quantified in the supernatants of zoledronic acid treated PC-3 and DU145 cells by using Human IL-6 ELISA Kit (Biosource International Inc., California, USA). The cells were plated on 24-well plates at a concentration of 10^5 cells per well and incubated for 24, 48 and 72 hours with increasing concentrations of zoledronic acid (1-100µM). Supernatants were collected for all culture conditions and analyzed for IL-6 levels using a standard ELISA kit according to manufacturer's instructions. Standard curve for quantification was plotted from values of IL-6 standards provided by kit. IL-6 levels in zoledronic acid treated cells were recalculated based on the IL-6 levels from untreated control cells at the end of treatment in order to compensate the differences due to cell number. The decrease in IL-6 levels was also confirmed by RT-PCR.

Expression of IL-6 mRNA - The effect of zoledronic acid on IL-6 mRNA level was investigated by RT-PCR. RNA samples from untreated controls and DU-145 treated cells were isolated by using High Pure RNA Isolation Kit (Roche Applied Science, Mannheim, Germany). Primers and probes were included in Roche LightCycler Primer set (Human Interleukin-6). The procedure was carried out as a single step method for reverse transcription from RNA to cDNA and subsequent quantification was made without opening the reaction tube. A Roche Light Cycler apparatus was used with the following sequence: denaturation at 95ºC for 10 minutes, then 35 cycles of amplifications for 10 s at 95ºC, 10 s at 68ºC, 16 s at 72ºC, and a final cooling step to 40ºC. The data were analyzed by the software of Roche LightCycler (1.5) Instrument.

Statistical analyses - All experiments were set up in triplicate and the results were expressed as mean ± standard deviation (SD). GraphPad PRISM software (version 5) (San Diego, CA, USA) was used for the analysis of data and graphic presentations. Student's t-test or ANOVA was used for comparisons.

RESULTS

The cytotoxic and apoptotic effects of zoledronic acid - PC-3 and DU145 cell lines were sensitive to ZA mediated cytotoxicity; the maximum cytotoxicity was achieved at 72 hour with 100µM concentration of ZA. The cytotoxicity was proportional with the increasing concentrations of ZA for both cell lines and the difference from untreated controls was statistically significant ($p < 0.05$). (Data not shown). ZA induced time- and dose-dependent apoptosis in both cell lines. Data for PC-3 cell line regarding apoptosis is given in Figure-1. For PC-3 cell line, Caspase 3/7 activity was significantly increased in ZA treated cells, compared to untreated controls ($p < 0.05$) (Figure-2).

IL-6 secretion as detected in the supernatants of PC-3 and DU145 cells - Incubation of PC-3 and DU145 cells with increasing concentrations of ZA for 24, 48 and 72 hours resulted in a significant dose-dependent decrease in IL-6 secretion ($p < 0.05$) (Figure-3 and 4). This effect was detected with the lowest dose and at the earliest time points. A difference in terms of dose-dependent inhibition of IL-6 secretion between two cell lines could only be observed at 72 hours. The lowest level of IL-6 secretion was achieved at 24 hours for PC-3 cells.

For DU-145 cells, a four-fold decrease in IL-6 secretion was found in ZA treated cells with 60 µM and higher concentrations, compared to untreated controls. However, for PC-3 cells, IL-6 secretion was only halved with the same concentrations and IL-6 secretion was significantly higher in DU145 cells than PC-3 cells ($p < 0.05$).

Interestingly, for PC-3 cell line, there was no association between the degree of apoptosis and inhibition of IL-6 secretion following ZA treatment, ($p = 0.347$). In contrast , for DU145 cells, the inhibition of IL-6 secretion was correlated with the degree of apoptosis ($p = 0.002$).

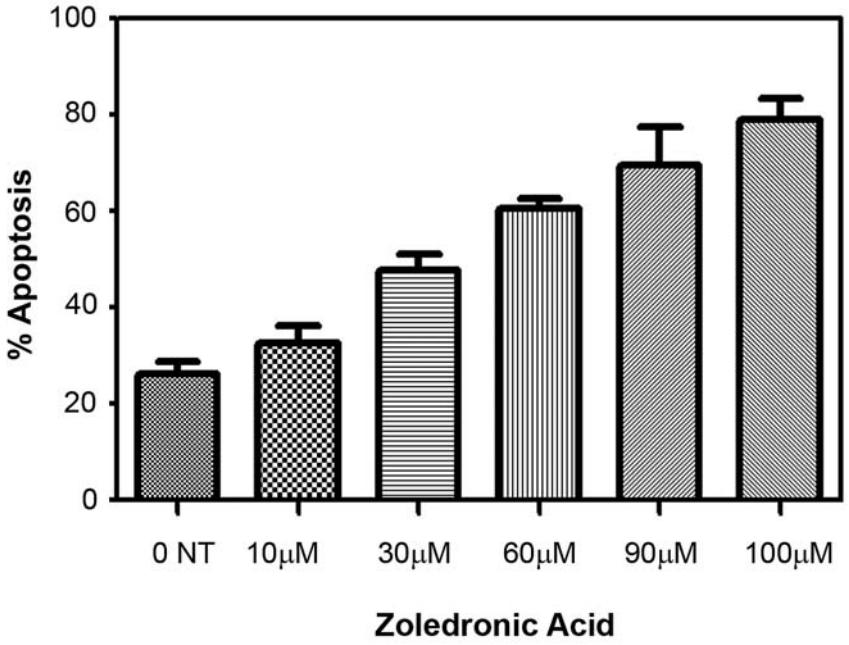


Figure 1 *– Concentration dependent relative apoptosis in PC-3 cell line following exposure to zoledronic acid. PC-3 cell line was treated with increasing concentrations of zoledronic acid for 72 hours and then the levels of mono-oligo nucleosome fragments was quantified using Cell Death Detection Kit. Columns, the means of two independent experiments; bars, SD. 0 NT, untreated controls. P < 0.05, vs. controls.*

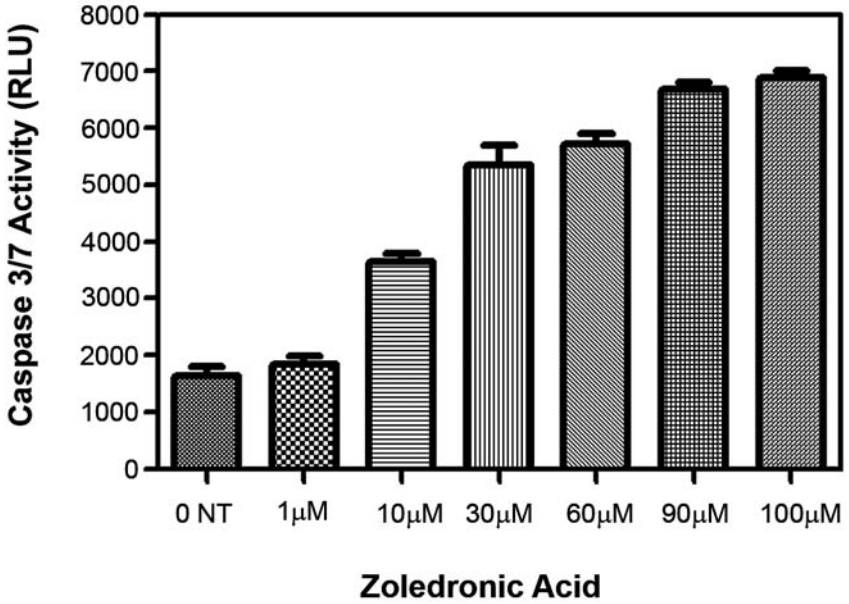


Figure 2 *– Concentration dependent caspase 3/7 activity in PC-3 cell line following exposure to zoledronic acid. PC-3 cell line was treated with increasing concentrations of zoledronic acid for 72 hours and then the levels of caspase 3/7 was measured using caspase-Glo 3/7 assay. Columns, the means of two independent experiments; bars, SD. 0 NT, untreated controls. P < 0.05, vs. controls.*

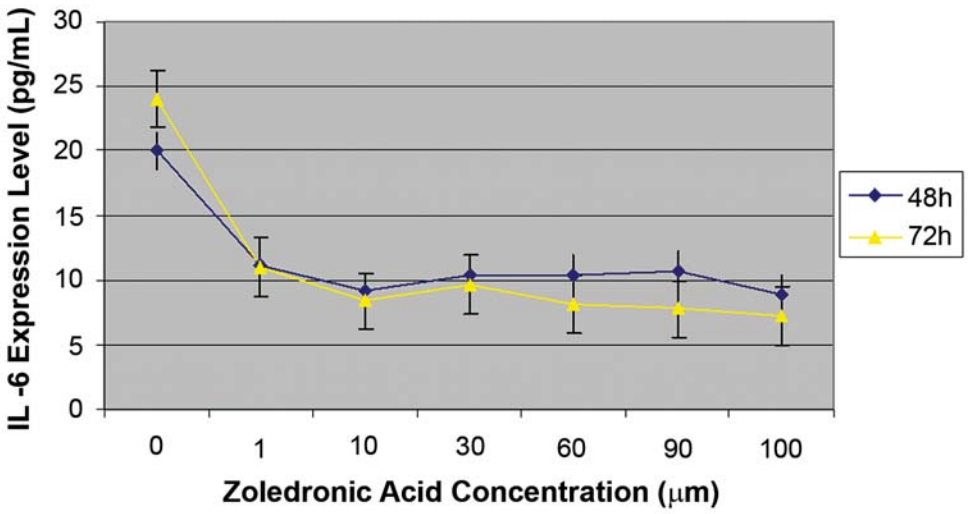


Figure 3 *– Effect of zoledronic acid treatment on IL-6 secretion in PC-3 cell line. 10^5 viable cell/well was treated with increasing concentrations of zoledronic acid. IL-6 levels were measured after 48 and 72 hours by ELISA in the supernatants of zoledronic acid treated cells. Points, the mean of at least three independent experiments; bars, SD. 0, untreated controls. P < 0.05, vs. controls.*

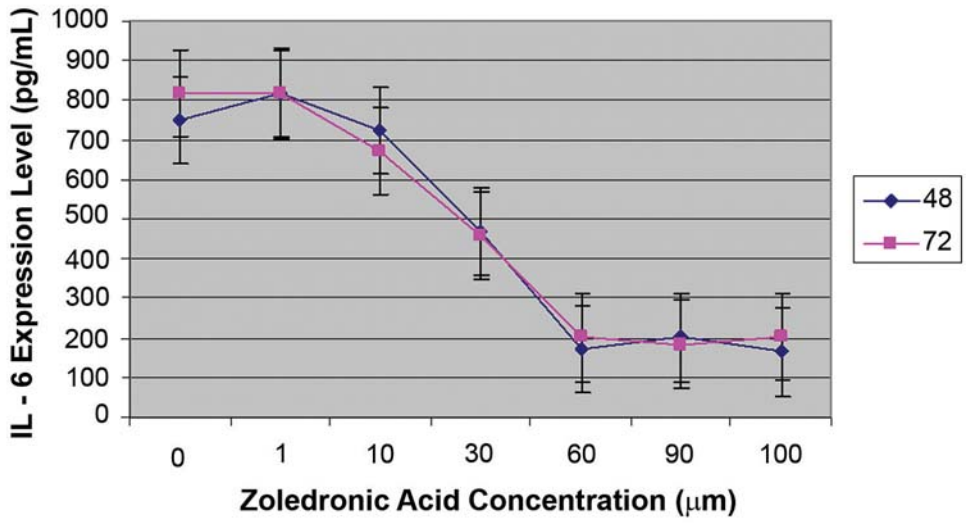
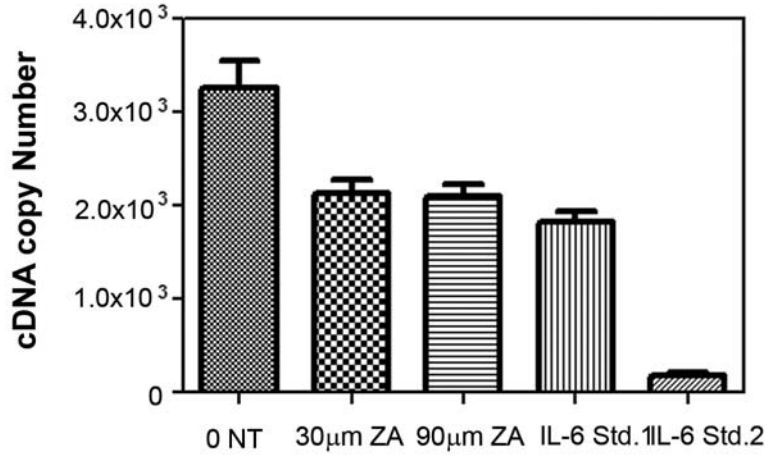


Figure 4 *– Effect of zoledronic acid treatment on IL-6 secretion in DU145 cell line. 10^5 viable cell/well was treated with increasing concentrations of zoledronic acid. IL-6 levels were measured after 48 and 72 hours by ELISA in the supernatants of zoledronic acid treated cells. Points, the mean of at least three independent experiments; bars, SD. 0, untreated controls. P < 0.05, vs. controls.*

Measurement of IL-6 mRNA levels in ZA treated DU145 cells by RT-PCR - RT-PCR was performed in DU-145 cells, in order to examine whether the reduction of IL-6 levels is associated with a decreased expression of IL-6 mRNA. The number of cDNA copies was significantly lower in DU-145 cells treated with 30 and 90μM ZA, compared to untreated controls ($p < 0.05$) (Figure-5).

A



B

Sample Name	Calculated Concentration	Crossing Point
0 NT	3.454E + 02	27.37
30 μM ZA	2.014E + 02	28.17
90 μM ZA	2.187E + 02	28.04
IL-6 Std.1(1.900E + 03)	1.900E + 03	24.85
IL-6 Std.2(1.900E + 02)	1.881E + 02	28.27

Figure 5 – *IL-6 mRNA expression levels of DU-145 cell line after zoledronic acid treatment. A) DU145 cell line was treated with 30 μM and 90μM concentrations of zoledronic acid for 72 hours and then IL-6 mRNA expression levels (as cDNA copy number) were measured by RT-PCR (Roche LightCycler 1.5 System). 0 NT, untreated controls. IL-6 std. 1 and 2 correspond to 1.900E + 03 and 1.900E + 02 copies of IL-6 mRNA, respectively. Columns, the mean of at least two independent experiments; bars, SD. P < 0.05, vs. controls. B) IL-6 standards were used for reference. Amplification of two standards allow the analysis of sample concentration.*

COMMENTS

The present study confirmed that ZA induces apoptosis in PC-3 and DU145 prostate cancer cell lines in a dose- and time-dependent manner. However, the extent of this effect was significantly different for PC-3 and DU145 cell lines. In addition, two cell lines differed in terms of IL-6 secretion. The degree of apoptosis was not related to the level of the inhibition of IL-6 secretion for PC-3 cells, which also secrete low levels of IL-6 compared to DU145 cells. On the other hand, the level of reduction in IL-6 secretion was correlated with the degree of ZA induced apoptosis in DU145 cell lines. Based on this data, it might be speculated that anti-tumoral effects of ZA could also be mediated by IL-6 and related signaling pathways in prostate cancer cells.

It has been well-documented that IL-6 is a multifunctional cytokine that plays an important role in the regulation of hematopoiesis, immune response, inflammation, bone metabolism and neural development (12). It is produced by different cells including lymphoid or non-lymphoid cells and malignant tissues (13). All prostate cells including normal prostate epithelia, cells originated from benign prostatic hyperplasia and malignant prostate cancer are shown to be capable of secreting IL-6 in cell cultures (14). Furthermore, increased secretion of IL-6 ligand and its receptors in serum has been reported for all stages of prostate cancer including hormone refractory pa-

tients (14,15). Also, clinical prognosis of prostate cancer is directly affected by serum IL-6 levels (15) and IL-6 plays an important role for the development of resistance to chemotherapeutics used in prostate cancer (16). Moreover, exogenous administration of IL-6 has been shown to inhibit doxorubicin-induced apoptosis in PC-3 cells (17).

In vitro studies demonstrated an increase in the proliferation of prostate cancer cells with IL-6 stimulation (18,19) and a decrease in growth rate of androgen insensitive PC-3 and DU145 cell lines treated with anti-IL-6 antibodies (16). These results suggest that the combined use of anticancer agents with drugs resulting in an inhibition of IL-6 expression could increase the efficacy of chemotherapy, particularly in patients with hormone refractory prostate cancer.

However, conflicting results have been reported regarding the stimulatory/inhibitory effects of IL-6 on the proliferation on various prostate cancer cell lines (11,20,21). These differences may be attributed to a several reasons related to IL-6 signaling pathway. Firstly, there are membranous and soluble forms of IL-6 ligand and its receptor, which are strictly regulated. Secondly, gp130, the signal transducer of IL-6 on the membrane, can be activated by various growth factors. Thirdly, activated gp130, either simultaneously or preferentially, triggers three intracellular pathways by the alteration of intracellular domain. IL-6 signaling is mediated by JAK-STAT, ras-raf-MAPK and PI3K-Akt signaling. It has been suggested that one or two alternative pathways are preferentially more active in different cell lines. IL-6 can also be up- and down regulated by autocrine or paracrine effects and feed-back mechanism (11,20,22,23). Its expression is regulated by several transcription factors such as AP-1, NFκB, CREB and c/EBP. It is considered that intracellular signaling pathways of IL-6 also regulate these transcription factors.

Zoledronic acid may affect a some molecules in signal transduction pathways including cell proliferation process (ras-raf-MAPK), tumor suppressor genes, apoptotic pathways, cell cycle proteins and posttranslational processes. Since ZA affects the binding of ras proteins to the membrane via protein prenylation (10), it might indirectly inhibit cell proliferation. In a recent study by Cavarretta et al., the effect of IL-6 was shown to be mediated by oncogene Mcl-1 (myeloid cell leukemia-1), an anti-apoptotic member of the Bcl-2 family in prostate cell line (24). The association between ZA treatment and IL-6 secretion may also be regulated by Mcl-1 expression.

Several authors have previously suggested that ZA cannot induce apoptosis (9,25). Such an inconsistency might be explained by the differences in ZA concentrations (25) and treatment durations (9). The present study indicates that a longer treatment period with higher concentrations of ZA is necessary to induce apoptosis. Interestingly, when bisphosphonates are combined with other common anti-neoplastic drugs, a significant synergy occurs. The synergic cytotoxic effect of ZA has previously been detected on prostate cancer cells (26,27).

Few studies investigated the relation between IL-6 expression/secretion and ZA treatment. A decreased IL-6 expression has been reported after ZA treatment in bone marrow stromal cells under in vitro conditions (28,29). On the contrary, a transient induction of an increase in TNF-alpha and IL-6 levels with ZA infusion has been demonstrated in cancer patients with fever (30). Although the disagreements between the studies may be explained by the variations of in vivo and in vitro conditions, all of these observations clearly points out that IL-6 has an important role in the processes related to both bone microenvironment and metastases in prostate cancer (31). The present study shows a correlation between the degree of ZA induced apoptosis and the inhibition of IL-6 secretion, implying that the apoptotic effect of ZA is associated with IL-6 and related pathways. Exogenous administration of IL-6 do not interfere the anticancer actions of ZA on PC-3 cells, which supports the above-mentioned association (17).

These findings raise two possible interpretations: either the reduction of IL-6 secretion itself induces the apoptotic process or it may be the outcome of ZA induced apoptosis in a dose dependent manner. If no significant correlation had been found between the decrease in IL-6 expression and the degree of apoptotic process, it could be suggested that ZA directly inhibits the autocrine mechanisms of IL-6 expression.

It would also be worth mentioning that ZA may indirectly induce apoptotic mechanisms through

affecting signal transduction pathways on the upstream region of apoptotic pathway. This probability may explain the reduction of IL-6 secretion with increased apoptosis, which was observed after ZA treatment in our study. Therefore, it can be suggested that ZA not only directly induces apoptotic pathways, but also indirectly affects one or more signal transduction molecules located on upstream region, which cause the apoptosis in PC-3 and DU145 cell lines. For these reasons, it is necessary to determine the target molecules that play key roles on the effects of ZA.

CONCLUSION

The present in vitro study shows a time- and dose-dependent apoptotic effect of ZA on both PC-3 and DU145 prostate cancer cell lines, which correlates with an inhibitory effect on IL-6 expression in DU145 cells. Additional research is required to further elucidate the activity of IL-6 and its role in the pathogenesis of advanced prostate cancer at cellular and molecular levels. Also, further studies are required to investigate the down regulation of oncogene Mcl-1 (myeloid cell leukemia-1), an anti-apoptotic member of the Bcl-2 family, which is regulated directly by IL-6 in ZA treated cells (24). The inhibition of IL-6 with anti-IL-6 antibody sensitizes androgen-independent prostate cancer cells to chemotherapeutic agents in vitro (32); thus, treatment modalities targeting IL-6 may have multiple advantages in prostate cancer patients who receive limited therapeutic and survival benefit from conventional treatment alternatives (18).

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

Interleukin-6 (IL-6) is an important regulator of cellular events in human prostate cancer. It has multifunctional effects on proliferation, apoptosis, and angiogenesis and is a target for novel therapies. Most studies were performed with the anti-IL-6 antibody CNTO 328 in vitro and in vivo (1-3). They have demonstrated differences in responsiveness to the antibody between these two different cell lines. The authors of the present paper show that zoledronic acid, that is used for late stage prostate cancer treatment, has a negative effect on IL-6 expression. This is a novel important aspect of action of that drug in human prostate cancer therapy. Since IL-6 is considered a survival factor in some but not all human prostate cancers, this therapy may increase rate of cell death. However, growth-inhibitory effects of IL-6 in selected cell lines were also observed. For that reason, it is important to determine who are the patients who will benefit from anti-IL-6 therapy in the future. In summary, the manuscript by Asbagh et al. is translationally relevant and may stimulate research on IL-6 regulatory effects in prostate cancer in the future.

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Letter to the Editor
International Braz J Urol Vol. 34 (3): 365-371, May - June, 2008

Re: Prognostic Relevance of the Histological Subtype of Renal Cell Carcinoma

Marcos F. Dall'Oglio, Alberto A. Antunes, Antonio C. Pompeo, Alcides Mosconi, Katia R. M. Leite, Miguel Srougi

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Int Braz J Urol, 34: 3-8, 2008

To the Editor,

Renal cell carcinomas are classified morphologically into 4 major categories by the current World Health Organization classification: clear cell (conventional), papillary, chromophobe and collecting duct (Bellini cell). These tumors seem to behave differently and numerous prognostic factors have been confirmed to be of utility in establishing predictive information, including tumor stage, renal sinus involvement and extra-renal spread. In addition, histopathological parameters have gained acceptance in routine clinical practice, being nuclear pleomorphism grading (in especial the Fuhrman method) one of the most common used. More recently, several studies have shown that chromophobe renal cell carcinoma has a significantly better prognosis than clear cell carcinoma. (4,7,8), with several series showing that this variant has more than 95% 5-year survival. These tumors often present as large masses, but the majority is organ confined (pT3 or pT4 chromophobe tumors are rare). Since morphologically many would qualify as Fuhrman grade 3, the nuclear grading does not reflect their prognosis and its use is not recommended in chromophobe tumors.

The interesting article by Dall'oglio et al describes a contemporary, single-institution series of renal tumors that may represent the largest study in a population from South America. (3) It is a well designed article that should greatly contribute to this interesting area of urological pathology. They found that clear cell, papillary and chromophobe types of renal cell carcinomas had 76.6, 71.1 and 71.2% and that sarcomatoid differentiation is highly correlated with aggressiveness. The reported relative poor prognosis of chromophobe renal cell carcinomas, however, represents a finding that is discrepant to studies from North America (1), Europe (2), Oceania (5) and Asia (6), when sarcomatoid carcinomas are excluded from the analyses. Several articles assessing prognosis of this subtype have found that even large tumors (mean diameter was 9 cm in one study) with "high" nuclear grade, behave better than other types. (1) The study brings new data to the discussion and shows that chromophobe renal cell carcinomas can behave bad in either selected populations or clinical scenarios, which remains to be elucidated. The authors raise the possibility that in the Brazilian population presentation at higher stages may contribute to this behavior. What the authors could have told the readers is whether multivariate analyses of the subtypes show prognostic differences independent of size, stage, renal sinus involvement and nuclear grade. Since the authors have retrospectively reviewed all cases, it should be easy to perform this analysis as all the other variables are in the standard pathology report. It would greatly increase the strength of the data and contribute to the better understanding on the behavior of renal cell tumors.

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Re: Laparoscopic Radical Prostatectomy: Omitting a Pelvic Drain

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Int Braz J Urol, 34: 151-158, 2008

To the Editor,

The placement of a drain post prostatectomy is the subject of much discussion these days. A lot has been made of surgeons moving to the non-drained model of prostatectomy, the goal has been to become less invasive and reduce patient morbidity. In open prostatectomy, the drain is placed via a separate stab incision while in laparoscopic or robotic cases the drain is brought out through a pre-existing port site. In both cases, the drain is usually removed at day one in a simple manner without any additional anesthesia. The purpose of a pelvic drain is to remove the abdominal fluid contents resulting from the surgery. This can be blood, lymph or urine. The point is what is the downside?

The drain provides an additional source of diagnostic information during the postoperative period and can help early diagnosis of postoperative problems. This is especially important in modern day surgery with patients going home in under 24 hours. Identifying potential bleeding or urinary extravagation can prevent readmissions and potentially more catastrophic complications. While some are proud of not having to use a drain post surgery, I am sure all would agree that they have at times had to place one

post surgery or have had postoperative bleeding or urinomas that have remained undrained.

Though there are a few studies, which have addressed the avoidance for, drain in open radical prostatectomy (1,2) there is only one paper that addressed the avoidance of drain following laparoscopic prostatectomy (3). This paper is a retrospective study concluding that drains may be placed selectively following laparoscopic radical prostatectomy. The authors subjectively omitted drain placement in 75% of 208 patients undergoing this operation with no ill effects. The surgeon chose to place drains based mainly on large bladder neck reconstructions or intraoperative anastomotic leak on saline bladder lavage. A randomized prospectively designed study with cystograms performed at a set time interval from surgery would give better evidence for this ongoing debate. A crucial endpoint for investigation would be the objective benefits of omitting drain placement such as validated assessment of postoperative patient discomfort.

Advantages claimed for avoidance of the drain have been decreased OR times, lack of pain at removal and shorter hospital stay (4). Advantages of drain placement at laparoscopic prostatectomy have been early recognition of inadequate hemostasis and urine leak while allowing efflux of blood, urine and lymphatic fluid from the pelvis. Drain placement may reduce hematoma formation, which has been shown to cause bladder neck contractures and permanent incontinence in a significant percentage of patients when they occur (5).

We believe that the simple drain is not only acceptable but also essential to allow early diagnosis of postoperative problems and to prevent more serious issues evolving. I would have to see good evidence of the benefits in omitting drains to consider changing this practice.

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REPLY BY THE AUTHORS

We appreciate the thoughtful critique by Dr. Patel and are pleased that our article has sparked continued debate on the subject of pelvic drain placement following minimally invasive prostatectomy. He raises several points of criticism to which we would like to respond.

First, Dr. Patel notes that surgeons are moving to the “non-drained model”. We do not support such a model, nor do we promote a sense of pride or cavalier behavior. Instead, we are promoting a selective drainage strategy. Furthermore, we believe that our selective drainage strategy as outlined in our

article contains much of the "good evidence" that Dr. Patel calls for to settle this question, since no patient had a complication related to absence of a drain, and cystograms were obtained in virtually all patients.

In the era of evidence-based medicine, the question, "What is the downside?" is misdirected. Instead of asking, "why not?" we should demand that there be a robust reason for each of our maneuvers. Having initially presented this data at regional and national meetings, we observed the tendency of surgeons who, deeply accustomed to their routine, looked at the data and then tossed it aside to rely on gut feelings. Instead, we need to look closely at each potential complication for which at the outset we believe a drain will raise a red flag.

Is a pelvic drain a reliable signal of serious hemorrhage requiring reoperation in the immediate postoperative period? Probably not. In our series, there were no cases of hemorrhage or hematoma. We have all seen patients brought back to the operating room for severe bleeding within the first 24 hours after prostatectomy in whom a clotted Jackson-Pratt drain adjacent to a large hematoma had zero output. Of course, if hemostasis is truly concerning and appropriate measures have been taken, a drain should be placed, as was done for 2 patients in our series. However, drain or no drain, patients with serious postoperative bleeding will display clinical signs including decreasing hemoglobin, hemodynamic instability, oliguria, or abdominal distension. In over 2,000 patients undergoing minimally invasive prostatectomy in our experience, we have yet to see a patient with bloody drain output as the sole indicator of evolving problems.

Does a pelvic drain signal impending lymphocele formation? Absolutely not. As Dr. Patel points out, most patients are discharged within 24 hours without drains. On average, lymphoceles present 2 - 4 weeks after surgery, long after the drain has been removed. Evacuation of lymphatic fluid and/or diagnosing impending lymphoceles should not generally be used as a justification for drain placement.

Potential urinary extravasation from the anastomosis is the main justification for drain placement. We believe that a selective strategy can correctly identify those patients at risk for urine leak. In the remaining patients, the drain is simply unnecessary, and a potential source of pain and anxiety for the patient. As regards patient perception of the drain, we agree that the endpoints of validated pain scores and directed questionnaires are lacking in our study.

Dr. Patel has correctly stated that a prospective study is required, in which cystograms are performed at a set interval from surgery. Our study, while retrospective, is the first in the literature to contain cystograms in virtually all patients (206/208, or 99%), most of which were done within the first week (90% of patients). However, we respectfully disagree with Dr. Patel's response in calling for randomization. Herein lies the key point: we do not advocate omitting drains in all patients, and randomizing patients to be drained or undrained would likely increase the incidence of undiagnosed complications. In fact, we advocate selection bias, in particular the bias of the senior surgeon. This is an active, selective strategy whereby drains are placed at the surgeon's discretion when concerns exist regarding the bladder neck, the anastomosis, or overall case complexity.

Our study adds to a growing body of literature that selective drain placement is likely to be required in 25% of cases (1-3). Can an experienced surgeon correctly identify the appropriate 1 out of 4 patients in whom drainage is required? Our data indicates the answer is definitely yes. Table 4 in our manuscript displays the true cystographic leak rate in the drained group is 15.6%, compared to 2.5% in patients where a drain was deemed unnecessary ($p = 0.002$). In the latter group, these were clinically insignificant extravasations, and no urinomas developed. This is reassuring evidence in support of a selective strategy for drain placement.

Having combined evidence from our own data and the other referenced studies, we have changed our practice. In the last 4 years, a selective drain placement strategy has not resulted in any measurable increase in morbidity. Readers need to decide individually how comfortable they are with this strategy and should not adopt this approach during the learning curve.

Respectfully,

The Authors

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Re: Gynecologic-Tract Sparing Extra Peritoneal Retrograde Radical Cystectomy with Neobladder

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Int Braz J Urol, 34: 180-190, 2008

To the Editor,

Bladder cancer is considered the most prevalent malignant tumor affecting male in Egypt. Orthotopic ileal neobladder is currently the preferred continent urinary diversion in suitable patients undergoing radical cystectomy for muscle-invasive bladder cancer and may be considered the gold standard with which other forms of diversion are compared. Incorporation of antireflux system in orthotopic ileal neobladder substitutes is important in protecting the upper urinary tract in all patients undergoing continent diversion with a reasonable life expectancy. If this were not important, why is it that normal human bladder anatomy has evolved with an effective antireflux mechanism? Indeed, many antireflux techniques have been developed but the multiplicity of these techniques suggests that an ideal solution has not been found. All antireflux anastmosis have an inherent risk of functional failure (1).

Patients with carcinoma in situ of the prostatic urethra, tumors near bladder neck or infiltrating the prostate, multifocal papillary tumors, history of upper tract tumors or positive margins on frozen section of the transected proximal urethra must be excluded. For these patients, continent cutaneous diversion using the same technique will be evolved soon. After radical cystectomy in females, both ureters are intussuscepted in modified Sigma pouch but most of the females now prefer orthotopic ileal neobladder (2).

The new technique, which prevents reflux, has several advantages compared with antireflux techniques: technical simplicity and the procedure is suitable for all types of ureters including normal, dilated, short and irradiated ureters. It allows a non obstructed unidirectional flow of urine with minimal rate of stenosis and/or surgical revision so; it can protect the upper urinary tract. The use of foreign material like staples or meshes is avoided and the antireflux system is constructed from a minimal length of bowel segment decreasing metabolic complications associated with malabsorption or resorption. The afferent short limb provides extra length to reach the ureter, a tension free anastomosis, no risks of ureteral angulation with neobladder filling, and the possibility to resect the ureter far above the bladder, thus avoiding ureteral ischemia and distal recur-

rence. With intermediate follow up the S pouch ileal neobladder incorporating the new antireflux technique appears to be effective in preventing reflux of urine without significantly increasing the incidence of obstruction. The clinical and functional results of S pouch ileal neobladder appear to be accepted. Despite these encouraging results prolonged follow up will be required to determine the durability and long term complications associated with orthotopic ileal neobladder.

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Men Reporting Lasting Longer with Hyperforin

To the Editor,

Premature ejaculation (PE) is a common, embarrassing and significantly under treated medical condition that affects men and their partners. Dapoxetine, a new short lasting selective serotonin reuptake inhibitor (SSRI), has demonstrated clinical efficacy in clinical trials when used immediately before intercourse (1). However, Dapoxetine has not yet been approved by the regulatory agency in part because of concern of risk and benefit ration of a SSRI in this quality of life condition.

We became interested if Hypericum perforatum, a natural supplement that has demonstrated pharmacologically to inhibit serotonin reuptake and can be formulated to help men last longer during sexual intercourse. In a rat model of ejaculation duration, hyperforin extract from Hypericum perforatum can delay time to ejaculation (2,3).

Ten male volunteers took the rapid release formulation of hyperforin (DeLithe Nutraceutical, In., Pittsburgh, PA) for 8 weeks and assessed their sexual intercourse duration and sexual satisfaction.

In 5 men with mean ejaculatory duration at baseline of less than 90 seconds (mean age 39 years old), 4 reported lasting longer - mean time to ejaculation before and after treatment, 58 ± 12 seconds to 131 ± 23 seconds, respectively ($p < 0.01$). Equally interesting, the mean sexual intercourse duration increased from 266 ± 39 to 391 ± 34 seconds ($p=0.02$) after Hyperforin extract treatment in 3 of 5 men with ejaculation greater than 3 minutes at baseline (mean age 43 years old). No adverse effect on sexual function and no systemic side effects were reported.

Seven of 10 couples reported subjective global sexual satisfaction improvement for both the men and his partner after hyperforin. Five couples reported more frequent female orgasm. Rapid onset of action, ease of use and safety make hyperforin extract an option for men who wish to last longer (4). Prospective randomized studies are necessary to further evaluation the utility of hyperforin extract.

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STONE DISEASE

Treatment of large impacted proximal ureteral stones: a prospective randomized comparison of percutaneous antegrade ureterolithotripsy versus retrograde ureterolithotripsy

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Purpose: We compared the safety and efficacy of percutaneous antegrade ureterolithotripsy with retrograde ureterolithotripsy for large impacted proximal ureter stones in a prospective randomized manner.
Materials and Methods: A total of 91 patients with large impacted proximal ureteral stones, defined as stones > 1 cm in size located between the ureteropelvic junction and the lower border of the fourth lumbar vertebra, were prospectively randomized for antegrade (44) or retrograde (47) ureterolithotripsy. Failure of the procedure (conversion to an open procedure), intraoperative and postoperative morbidity, operative time, hospital stay, stone clearance at discharge home, and follow-up were analyzed in each group.
Results: The main complications were bleeding (2.3%; 1 of 43) for the antegrade procedure and ureteral injury (2.3%; 1 of 44) for the retrograde procedure. Percutaneous antegrade ureterolithotripsy was associated with longer operative times (75.4 ± 11.8 v 30.6 ± 7.8 minutes; $P < 0.001$), longer hospital stay (6.3 ± 0.5 v 2.1 ± 0.4 days; $P < 0.001$), and a longer interval to return to normal activities (7.8 ± 0.7 v 2.7 ± 0.6 days; $P < 0.001$). Nevertheless, the percutaneous antegrade procedure had a higher stone-free rate both at discharge home (95.3% v 79.5%; $P = 0.027$), and 1 month post-procedure (100% v 86.4%; $P = 0.026$).
Conclusions: Percutaneous antegrade ureterolithotripsy is a valuable treatment modality for impacted proximal ureteral calculi larger than 1 cm, and achieves higher stone-free rates than those of retrograde ureteroscopy with holmium:YAG laser lithotripsy. The drawbacks of the antegrade procedure are longer operative time and hospital stay.

Editorial Comment

This study reported higher success with antegrade versus retrograde ureteroscopy for large proximal ureteral stones. The authors should be commended for a well-executed randomized clinical trial that addresses an important question. However, the addition of flexible ureteroscopy to their retrograde approach may have changed the outcome.

The authors did not utilize flexible ureteroscopy during their retrograde approach - this might impact the stone-free success rate. It would have been helpful to report the size and location of the residual stones - if indeed they were fragments that had migrated to the kidney, these would have been possible to address with the addition of flexible ureteroscopy and stone retrieval. Similarly, flexible ureteroscopy may have facilitated reaching the stone in the 6% of patients who failed the retrograde approach.

The authors did not utilize flexible nephroscopy for their antegrade approach. This might have allowed the use of a lower pole access, with subsequent lower morbidity (pain, hospital stay, return to normal activities). It would be useful to try to establish predictive factors for failure of the retrograde approach - one might hypothesize that male gender, more proximal location, and high grade obstruction would predispose to either stone migration of difficulty accessing the stone. Lastly, one might consider the use of devices to prevent stone migration, such as the Boston Scientific Stone Cone, Cook N-Trap or PercSys Accordion in the setting of large proximal ureteral stones.

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Impact of percutaneous nephrolithotomy on estimated glomerular filtration rate in patients with chronic kidney disease

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Background and Purpose: We investigated the impact of percutaneous renal procedures on estimated glomerular filtration rate (GFR) of patients with chronic kidney disease (CKD). Patients and Methods: The GFRs of adult patients were calculated using the Modification of Diet in Renal Disease formula, and the patients were staged according to the Kidney Disease Outcome Quality Initiative CKD classification system. The study included 185 patients with preoperative GFR values less than 60 mL/min/1.73 m(2). The impact of percutaneous nephrolithotomy (PCNL) on GFR was analyzed by comparing the preoperative GFR with the GFR before discharge and at postoperative month 3.
Results: Patients with CKD had a significant increase in the GFR after the procedure. In postoperative month 3, the mean GFR was more than 60 mL/min/1.73 m(2) in 25% of the patients with CKD and less than 60 mL/min/1.73 m(2) in 75%. While all patients with stage 5 CKD improved to better stages, some other patients' conditions declined to stage 5 from better stages at the end of postoperative month 3. No patient needed dialysis. The presence of urinary tract infections tended to affect GFR negatively. Conclusion: Estimated GFR, as a better indicator of renal function, is significantly affected by the PCNL procedure. While significant improvement was observed in late-stage patients with CKD, unexpected deterioration could occur in patients at earlier stages.

Editorial Comment

The investigators studied a challenging patient population - the high rate of staghorn calculi and high rate of multiple accesses suggest a complex stone burden. This certainly may account for the high complication rates, specifically related to transfusion, sepsis and death. Alternatively, it is possible that the CKD could impact platelet function, baseline hemoglobin, cell-mediated immunity and humoral defenses. It is possible that the higher rate of urinary leak could be related to the thinned renal parenchyma in CKD. Interestingly, number of renal accesses or presence of a solitary kidney did not predict a negative outcome on GFR. Intuition would suggest that in these high risk patients, a greater reliance on flexible ureteroscopy and nephroscopy to decrease the need for multiple accesses might be warranted. One can conclude that GFR often improves after PCNL, however occasionally renal function will worsen. Patients should be counseled on the 25% chance of improvement and 4% risk of deterioration.

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ENDOUROLOGY & LAPAROSCOPY

Comparison of open and laparoscopic nephrectomy in obese and nonobese patients: outcomes stratified by body mass index

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Purpose: Laparoscopic radical nephrectomy has been accepted as the preferred management for low stage renal masses not amenable to partial nephrectomy. Early in the mid 1990s several studies suggested that obesity should be a relative contraindication to laparoscopy. We present our surgical outcomes and complications in patients undergoing open and laparoscopic nephrectomy, stratified by body mass index. Materials and Methods: We retrospectively identified 88 patients, of whom 43 underwent open nephrectomy and 45 were treated laparoscopically. All patients were stratified by body mass index to compare multiple perioperative end points and pathological outcomes of laparoscopy.
Results: Overall our data showed that compared to open nephrectomy laparoscopic nephrectomy resulted in statistically significant lower estimated blood loss (147.95 vs. 640.48 cc, $p < 0.0002$), operative time (156.11 vs. 198.95 minutes, $p < 0.003$) and hospital stay (3.7 vs. 5.9 days, $p < 0.004$). When stratified by body mass index less than 25, 25 to 29.9 and 30 kg/m(2) or greater, there was a statistically significant difference in estimated blood loss and hospital stay that was in favor of the laparoscopic approach in each body mass index category. Operative time did not show a statistical difference in the subgroups but all laparoscopic procedure times were shorter than open procedure times in each body mass index category. When patients with a body mass index of greater than 30 kg/m(2) were further subgrouped into 35 kg/m(2) or greater and 40 kg/m(2) or greater, there was a statistically significant difference in estimated blood loss and hospital stay that was again in favor of the laparoscopic method.
Conclusions: Laparoscopic radical nephrectomy is technically more challenging as body mass index increases due to many factors but our data show that it is feasible and safe in experienced hands. Laparoscopy appears to result in perioperative outcomes that are superior to those of open nephrectomy in this high risk population with a complication profile that is equivalent to that of the open method for each stratified body mass index category.

Editorial Comment

Historically, obesity has been considered a relative contra-indication for laparoscopic surgery. Recently, experienced laparoscopic surgeons have demonstrated the benefits of laparoscopic approach, particularly on this population of patients.

The authors have demonstrated on this retrospective study that obese patients undergoing laparoscopic radical nephrectomy had less blood loss and decreased operative time than the cohort open nephrectomy patients. Moreover, the increase in operative time for the laparoscopic approach was calculated as 7.56 minutes per BMI in average, while the mean operative time difference was 38.9 minutes less than an open procedure. In conclusion, the laparoscopic approach has been shown to offer several advantages especially to the obese population.

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The impact of minimally invasive techniques on open partial nephrectomy: a 10-year single institutional experience

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Purpose: With the advent of minimally invasive, nephron sparing surgical options we hypothesized that the indications, perioperative parameters and complication rates of open partial nephrectomy may have changed significantly during a 10-year period. Materials and Methods: Open partial nephrectomy was compared during 2, 3-year periods. From 1994 to 1996 (before laparoscopic partial nephrectomy, cryoablation and radio frequency ablation) 208 cases were compared vs. 347 open partial nephrectomies performed from 2004 to 2006 with regard to indications, perioperative parameters and complication rates.
Results: There were no significant differences between the groups with regard to age (59 vs. 58 years), gender (65.5% vs. 65.0% male) and tumor size (3.9 vs. 3.6 cm). Tumors removed in the recent era were more often in a solitary kidney (40.0% vs. 15.6%) and centrally located (55.6% vs. 37.3%), and pathological evaluation more often revealed higher grade (Fuhrman 3 or 4) (43.1% vs. 27.8%, each $p < 0.0001$). Despite increased technical difficulty ischemia time in the more recent era was shorter (19.1 vs. 40.6 minutes, $p = 0.0000$), and the urological and overall complication rates were statistically similar (7.5% vs. 8.9%, $p = 0.6071$ and 19.1% vs. 14.4%, $p = 0.1723$, respectively).
Conclusions: At a tertiary referral center the introduction of minimally invasive, nephron sparing surgical techniques has drawn away less complicated, less aggressive tumors, reserving the bulk of more complicated central tumors for open partial nephrectomy without decreasing the total number of open cases. With experience these more difficult central tumors are being successfully treated with decreased warm ischemia time and complication rates that are comparable to those in historical series.

Editorial Comment

This retrospective study demonstrated that the outcomes of the management of small renal masses in a high volume tertiary care institution were consistent when oncological principles were followed despite the different minimally invasive techniques were applied to treat these masses.

The open partial nephrectomies were reserved to manage more complicated central masses, while the laparoscopic approach allowed small masses to be managed with nephron-sparing techniques, including ablative technology.

The overall number of open procedures remained the same, as well as the level and number of complications for both open and minimally invasive approaches.

Once again, the authors demonstrated that when the basic oncological principles are followed and a systemic protocol evaluates patients for complex minimally invasive surgery, experienced surgeons could attain comparable results as historically established open surgery in a high volume tertiary care institution.

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IMAGING

The incidental adrenal mass on CT: prevalence of adrenal disease in 1,049 consecutive adrenal masses in patients with no known malignancy

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AJR, Am J Roentgenol 2008; 190: 1163-1168

Purpose: The purpose of our study was to determine the nature and prevalence of adrenal lesions identified on CT in patients with no known malignancy.
Materials and Methods: A computer search of abdominal CT reports using the term "adrenal" was performed in 65,231 consecutive patients with examinations performed from January 2000 to December 2003. An adrenal mass was identified in 3,307 (5%) patients. Patients with no known malignancy and no suspicion for a hyperfunctioning adrenal mass were further isolated. Nine hundred seventy-three patients with 1,049 adrenal masses fulfilled the study criteria. The nature of each lesion was determined by histopathology; imaging characterization with CT, MRI, or washout; a minimum of 1 year of stability on follow-up imaging; or clinical follow-up of at least 2 years.
Results: One thousand forty-nine adrenal masses were characterized with the following methods: histopathology (n = 12), imaging characterization (n = 909), imaging follow-up (n = 87), and clinical follow-up (n = 41). There were 788 adenomas constituting 75% of all lesions. There were 68 myelolipomas (6%), 47 hematomas (4%), and 13 cysts (1%). Three pheochromocytomas (0.3%) and one cortisol-producing adenoma (0.1%) were found incidentally. One hundred twenty-eight lesions (12%) were presumed to be benign by imaging or clinical stability. No malignant adrenal masses were found, even among the 14 patients who later developed malignancy elsewhere.
Conclusions: In 973 consecutive patients with an incidental adrenal mass and no history of cancer, no malignant lesions were identified. Adenomas (75%) and myelolipomas (6%) were the most common lesions.

Editorial Comment

The authors report very large retrospective study regarding the prevalence of adrenal incidentalomas on CT studies performed in patients without cancer. Actually this publication encompasses a larger number of patients when compared with previous study published by the same authors where all of the incidentally detected adrenal masses with a CT attenuation of equal or less than 10 HU were benign (1). Adrenal incidentalomas were classified almost exclusively by classical and well known imaging criteria (unenhanced and enhanced CT studies and chemical-shift MR imaging). Although the authors reports that only 1% of the adrenal masses of this large series was histological evaluated , their criteria has been proved to be effective by other large series where histological confirmation were obtained(2,3). As radiologic experience accumulates, the tendency to accept strict and specific imaging features for adequate characterization of adrenal adenomas continues to grow. Large series with histological confirmation, large number of patients without histological confirmation but with prolonged clinical and radiological follow-up continues to strength the role of imaging features in the evaluation of adrenal adenomas. In many centers, radiologic characterization of adrenal adenomas is accepted similarly to the radiologic characterization of other adrenal incidentalomas such as cysts, pseudocysts, hematomas and mielolipomas .Small, < 3 cm in diameter, homogeneous and well defined adrenal mass with CT attenuation of equal or less than 10 HU or showing more than 20% of loss of signal intensity on chemical-shit MR imaging should be considered as an adrenal adenoma.

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Endorectal and dynamic contrast-enhanced MRI for detection of local recurrence after radical prostatectomy

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Objective: The objective of our study was to evaluate the sensitivity and specificity of endorectal MRI combined with dynamic contrast-enhanced MRI to detect local recurrence after radical prostatectomy.
Materials and Methods: A total of 51 patients who had undergone radical prostatectomy for prostatic adenocarcinoma 10 months to 6 years before underwent a combined endorectal coil MRI and dynamic gadolinium-enhanced MRI before endorectal sonographically guided biopsy of the prostatic fossa. The MRI combined with MR dynamic imaging results were correlated with the presence of recurrence defined as a positive biopsy result or reduction in prostate-specific antigen level after radiation therapy.
Results: Overall data of 46 (25 recurred, 21 nonrecurred) out of 51 evaluated patients were analyzed. All recurrences showed signal enhancement after gadolinium administration and, in particular, 22 of 24 patients (91%) showed rapid and early signal enhancement. The overall sensitivity and specificity of MR dynamic imaging was higher compared with MRI alone (88%, [95% CI] 69–98% and 100%, 84–100% compared with 48%, 28–69% and 52%, 30–74%). MRI combined with dynamic imaging allowed better identification of recurrences compared with MRI alone (McNemar test: chi-square1 = 16.67; p = < 0.0001).
Conclusion: MRI combined with dynamic contrast-enhanced MRI showed a higher sensitivity and specificity compared with MRI alone in detecting local recurrences after radical prostatectomy.

Editorial Comment

The authors of this manuscript confirms previous publications that has been shown that endorectal magnetic resonance imaging studies are of value for adequate characterization of local recurrence of prostate cancer after radical prostatectomy . Recurrent prostate cancer appears on dynamic contrast magnetic resonance imaging as an abnormal soft tissue mass with faster and stronger contrast enhancement and contrast washout. As we know the management of the patient with PSA recurrence after radical prostatectomy is debatable. In our daily practice, urologists and radiotherapists only sporadically require imaging in patients suspected of prostate cancer recurrence. Unless patient presents with positive digital rectal examination, they usually rely on

PSA kinetics. Even when anastomotic biopsies document only benign tissue, the study of PSA doubling time is usually characteristic of the coexistence of residual cancerous cells. Local recurrence of prostate cancer is usually clinically suspected based on PSA kinetics and is usually characterized by a prolonged doubling time (>10 months) in a patient with a Gleason score of 2–7, a positive surgical margin, and absence of seminal vesicles or lymph nodes involvement. Currently these patients may be treated by means of radiation therapy. In our experience both color Doppler transrectal ultrasound and dynamic contrast enhanced MR, followed by TRUS-guided biopsies are useful modalities for early detection and confirmation of local recurrence of prostate cancer. These modalities however, should be used only when confirmation of local recurrence of prostate cancer is mandatory or in other words will modify the patient's clinical management.

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UROGENITAL TRAUMA

Urethral and bladder neck injury associated with pelvic fracture in 25 female patients

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J Urol. 2006; 175: 2140-4

Purpose: We describe the presentation, diagnostic evaluation, management and outcome of female urethral trauma.
Materials and Methods: All female patients treated at Harborview Medical Center between 1985 and 2001 with urethral injury were identified by International Classification of Diseases 9th revision code. Approval of the Human Subject Division was obtained and patient charts were reviewed. The Urogenital Distress Inventory Short Form, the Incontinence Impact Questionnaire Short Form and the Female Sexual Function Index were sent to the patients.
Results: A total of 25 patients (13 adults, 12 children) with a mean age of 22 years (range 4 to 67) met inclusion criteria. All had pelvic fracture related to blunt trauma. They represented 6% of all female patients treated in the same review period with pelvic fracture. Blood was seen at the introitus in 15 patients and 19 had gross hematuria. Of the injuries 9 were avulsions, 15 were longitudinal lacerations and 1 was not further specified. Primary repair was performed in 21 patients and 4 were treated nonoperatively. There were 5 patients who required secondary procedures including fistula repair in 4 and continent urinary diversion in 1. At a mean followup of 7.3 years (range 1.6 to 14.4) 9 of 21 patients (43%) had moderate or severe lower urinary tract symptoms and 8 of 13 (38%) had sexual dysfunction (FSFI score less than 26.55). Conclusions: Female urethral and bladder neck injury occurs with pelvic fracture, presents with gross hematuria and/or blood at the introitus, and requires operative repair for avulsions and longitudinal lacerations. These patients are at risk for significant sexual and lower urinary tract dysfunction.

Pelvic fracture urethral injuries in girls

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J Urol. 2001; 165: 1660-5

Purpose: Injuries to the female urethra associated with pelvic fracture are uncommon. They may vary from urethral contusion to partial or circumferential rupture. When disruption has occurred at the level of the proximal urethra, it is usually complete and often associated with vaginal laceration. We retrospectively reviewed the records of a series of girls with pelvic fracture urethral stricture and present surgical treatment to restore urethral continuity and the outcome.
Materials and Methods: Between 1984 and 1997, 8 girls 4 to 16 years old (median age 9.6) with urethral injuries associated with pelvic fracture were treated at our institutions. Immediate therapy involved suprapubic cystostomy in 4 cases, urethral catheter alignment and simultaneous suprapubic cystostomy in 3, and primary suturing of the urethra, bladder neck and vagina in 1. Delayed 1-stage anastomotic repair was performed in 1 patient with urethral avulsion at the level of the bladder neck and in 5 with a proximal urethral distraction defect, while a neourethra was constructed from the anterior vaginal wall in a 2-stage procedure in 1 with mid urethral avulsion. Concomitant vaginal rupture in 7 cases was treated at delayed urethral reconstruction in 5 and by primary repair in 2. The surgical approach was retropubic in 3 cases, vaginal-retropubic in 1 and vaginal-transpubic in 4. Associated injuries included rectal injury in 3 girls and bladder neck laceration in 4. Overall, postoperative followup was 6 months to 6.3 years (median 3 years).
Results: Urethral obliteration developed in all patients treated with suprapubic cystostomy and simultaneous urethral realignment. The stricture-free rate for 1-stage anastomotic repair and substitution urethroplasty was 100%. In 1 girl, complete urinary incontinence developed, while another has mild stress incontinence. Retrospectively the 2 incontinent girls had had an associated bladder neck injury at the initial trauma. Two recurrent vaginal strictures were treated successfully with additional transpositions of lateral labial flaps.
Conclusions: This study emphasizes that combined vaginal-partial transpubic access is a reliable approach for resolving complex obliterative urethral strictures and associated urethrovaginal fistulas or severe bladder neck damage after traumatic pelvic fracture injury in female pediatric patients. Although our experience with the initial management of these injuries is limited, we advocate early cystostomy drainage and deferred surgical reconstruction when life threatening clinical conditions are present or extensive traumatized tissue in the affected area precludes immediate ideal surgical repair.

Editorial Comment

The above two articles illustrate the difficulty in diagnosing and managing the complications of female urethral injury from pelvic fracture. Such injuries can occur in up to 6% of all female pelvic fractures. Obviously, life threatening pelvic fractures and associated injuries need to be stabilized and reduced first, as part of traumatic resuscitation.

Female urethral injuries from pelvic fracture are due to severe mechanisms of injury, with many injuries being urethral disruption injuries. Female urethral injuries are mainly bladder neck injuries that extend into the urethra and/or avulsion injuries. Presenting signs of urethral injury are blood at the introitus or gross hematuria. Avulsion injuries are mostly diagnosed upon attempted catheterization. Associated vaginal injury in very common (up to 87%) and ranges from an anterior vaginal wall laceration to circumferential disruption. Despite the above, up to 40% of female urethral injuries are missed at the time of injury. A high index of suspicion is key to making the diagnosis reliably. In the acute setting we advocate immediate repair of the urethral and the vaginal injuries, since if only a supra-pubic tube is placed, the urethra typically obliterates, or urethrovaginal fistula and/or vaginal stenosis results. Bladder neck injuries should also be repaired in the early post injury period (up

to 2 weeks after) in order to prevent subsequent incontinence. Extensive surgical reconstruction is otherwise needed for such patients. If the patient is unstable, repair can often wait a few days until she is stable.

In prepubertal girls, where the pelvis is narrow and space limited, repair of urethral stenoses is very difficult. Often times, a combined vaginal and abdominal approach in needed for successful reconstruction – and often may require a partial or total pubectomy. In such cases, an interposition flap of omentum is important to prevent bladder and bowel herniation.

If the patient is incontinent after injury or repair, the urethra is typically fixed and rigid. In such cases, we have placed a bladder neck artificial sphincter, with good dryness. Unfortunately, the bladder is often too scarred to mobilize the bladder enough to do a bladder neck reconstruction, such as a Kropp or Young Dees Leadbetter

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PATHOLOGY

Partial atrophy on prostate needle biopsy cores: a morphologic and immunohistochemical study

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Partial atrophy is the most common benign mimicker of prostate cancer on needle biopsy. Of 3916 prostate needle core biopsy cases received in our consultation service over a period of 3 months (March 1, 2007 to May 31, 2007), 170 cases (4.3%) with partial atrophy were diagnosed as atypical glands by outside pathologists and prospectively identified. We supplemented our material with 108 cases of partial atrophy sent to our consultation service in 2006 from a single institution, which frequently uses a triple cocktail stain [p63, high molecular weight cytokeratin (HMWCK), alpha-methyl acyl-Coa racemase (AMACR)]. The morphologic features of the 278 cases and immunohistochemistry of 236 cases (198 with prostate cocktail and 38 with only basal cell makers) were analyzed. Forty-eight of 278 (17.3%) partial atrophy cases were mixed with postatrophic hyperplasia. Enlarged nuclei were visible in 43/278 (15.5%) cases, with prominent nucleoli seen in 58/278 (20.9%) cases (30 cases associated with nuclear enlargement). Of 198 cases with a prostatic cocktail stain, 48 (24.2%) had a cancer pattern for both basal cells and AMACR (p63-, HMWCK-, and AMACR+), 14 (7.1%) had a cancer pattern for basal cells (p63-, HMWCK-, and AMACR-), 89 (44.9%) had a cancer pattern for AMACR (p63+, HMWCK+, and AMACR+), and 47 (23.7%) had a totally benign pattern (p63+, HMWCK+, and AMACR-). Of the 198 cases using the cocktail stain, 136 (68.7%) had positive basal cell staining. The percentage of basal cells labeled with the combination of p63/HMWCK was: < 5% in 42 (21.2%) cases, 5% to 75% in 58 (29.3%) cases, and > 75% in 36 (18.2%) cases. An additional 38 cases immunostained only for p63 and/or HMWCK was negative in 2 (5.2%) cases, < 5% (13.1%) in 5 cases, 5% to 75% in 19 (50%) cases, and > 75% in 12 (31.6%) cases. In conclusion, partial atrophy is a benign mimicker of adenocarcinoma both as a result of its routine morphologic features and its immunohistochemical profile. Recognition of the classic morphology of partial

atrophy on routine hematoxylin and eosin-stained sections is critical to avoid misdiagnosing partial atrophy as adenocarcinoma.

Editorial Comment

The most common benign lesion that causes difficulty in the differential diagnosis with adenocarcinoma of the prostate is partial atrophy. This lesion was reported in the periodic literature in 1998 (1). Architecturally, partial atrophy consists of crowded glands often with a disorganized growth pattern. In contrast to complete atrophy, which can typically be diagnosed at scanning magnification owing to the presence of well-formed glands with a very basophilic appearance, partial atrophy has pale cytoplasm lateral to the nuclei giving rise to pale staining glands that more closely mimic cancer. Characteristically the basal cells are discontinuous and in some acini may be absent. An additional factor that contributes to the difficulty in distinguishing cancer from partial atrophy is the positivity for AMACR (α-methylacyl coenzyme A racemase) in some acini. In a recent study in our institution, we used the cocktail AMACR+34βE12 for analyzing the immunohistochemistry expression of a total of 727 acini on needle prostatic biopsies corresponding to 324 adenocarcinoma acini, 213 normal acini, and 190 partial atrophy acini. Adenocarcinoma acini showed weak, or strong expression of AMACR in 73/324 (22.5%), and 251/324 (77.5%) acini, respectively; normal acini showed negative, weak, or strong expression in 167/213 (78.4%), 33/213 (15.5%), and 13/213 (6.1%) acini, respectively; and foci of partial atrophy showed negative, and weak expression in 143/190 (75.3%), and 47/190 (24.7%) acini, respectively. No acini in partial atrophy showed strong expression. The distribution of basal cells in partial atrophy was continuous, discontinuous, and absent in 42/190 (22.1%), 104/190 (54.7%), and 44/190 (23.2%) acini, respectively. The absence of basal cells in 44/190 (23.2%) of partial atrophy foci, makes the use of AMACR attractive for the differential diagnosis. No strong positivity was seen in partial atrophy acini, however, the weak positivity seen in approximately 25% of the acini may be a pitfall for the correct interpretation. Furthermore, normal acini may show strong expression of AMACR in approximately 5% of the acini.

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Aberrant diffuse expression of p63 in adenocarcinoma of the prostate on needle biopsy and radical prostatectomy: report of 21 cases

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Aberrant diffuse expression of p63 in prostate carcinoma cells is a rare and poorly understood phenomenon. We studied 19 cases of prostate cancer with aberrant diffuse expression of p63 on needle biopsy and reviewed the subsequent radical prostatectomies in 6 cases. In 19/21 cases, 100% of the cancer nuclei stained intensely for p63, with 70% staining in the remaining 2 cases. Two additional radical prostatectomies with aberrant p63 staining with no needle biopsies available for review were also analyzed. On the hematoxylin and eosin-stained

slides, 19/21 cases (90.5%) showed a distinctive morphology composed predominantly of glands, nests, and cords with atrophic cytoplasm, hyperchromatic nuclei, and visible nucleoli. Needle biopsy cases ranged from Gleason patterns 3 to 5 with tumor identified on one or more cores, ranging from a minute focus to 80% of the core. In all 8 radical prostatectomies p63 positive cancer was present, with in 2/8 cases both p63 positive cancer and usual p63 negative acinar prostate cancer. In all 8 cases, the tumors were organ confined with negative margins and there was no seminal vesicle involvement or lymph node metastasis. The presence of p63 positive atypical glands with an infiltrative pattern and perineural invasion on radical prostatectomy confirmed the needle biopsy diagnosis of carcinoma. Rarely, prostate cancer can aberrantly express diffuse p63 staining in a nonbasal cell distribution leading to the erroneous diagnosis of atrophy or atypical basal cell proliferation. The diagnosis of prostate cancer is based on the morphology and confirmed by the absence of high molecular weight cytokeratin staining and positivity for alpha-methylacyl-CoA racemase in the atypical glands. Pathologists need to be aware of this rare and unusual phenomenon, which is a potential pitfall in prostate cancer diagnosis.

Editorial Comment

Pathologists use immunohistochemistry for the differential diagnosis between adenocarcinoma of the prostate and benign mimickers in difficult cases. The aim is to detect basal cells which excludes adenocarcinoma (1). The most frequently used markers for basal cells is clone 34βE12 (a pool of high-molecular-cytokeratins 1,5,10,11 and 14) and p63. 34βE12 stains the cytoplasm and p63 stains the nucleus of basal cells.

The cases of adenocarcinoma with aberrant expression of p63 studied by Osunkoya et al. is a very important finding. Pathologists need to be aware of this rare and unusual phenomenon, which is a potential pitfall in prostate cancer diagnosis.

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INVESTIGATIVE UROLOGY

Visualization of the neurovascular bundles and major pelvic ganglion with fluorescent tracers after penile injection in the rat

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BJU Int. 2008; 101: 1048-51

Objective: To evaluate whether fluorescent tracers can consistently label the neurovascular bundles (NVBs) and major pelvic ganglion (MPG) after an intracavernosal penile injection, as the reported incidence of

erectile dysfunction (ED) in men after radical prostatectomy (RP) is 55-65% and thus preservation of erectile function, sparing one or both of the NVBs remains one of the most vital factors.
Materials And Methods: Male Sprague-Dawley rats (3 months old) received penile injections (20 microL; seven rats/group) of either deionized water (DW), Fluoro-Gold (FG), Fast-Blue (FB), Fluoro-Ruby (FR) or green fluorescent pseudorabies virus (GF-PRv). The rats were killed at 2, 3 and 14 days after injection and the NVBs and MPG were harvested and placed directly under fluorescence light. Image analysis was done by computer, coupled to a microscope equipped with a digital camera. Each NVB and MPG were analysed for its staining pattern and consistency.
Results: When compared with the FB, FR and GF-PRv rats, the FG-injected rats had better staining of the NVB at 2, 3 and 14 days after injection. Under x200, FG highlighted the axons of the cavernous nerve (CN) and cell bodies (MPG). This indicates that FG injection into the penis induced the strongest CN labelling (positive staining) at 2 and 3 days after injection as compared with FB-, FR- and GF-PRv-injected rats.
Conclusion: FG injection into the penis has consistent retrograde staining of the NVBs and MPG after 3 days. Therefore, we predict that FG could potentially be used to improve the identification of the NVB in other models. However, further studies need to be carried out before these tracers can be used in humans.

Editorial Comment

This is an interesting and promising study where the authors aimed to evaluate whether various tracer substances can consistently label the neurovascular bundles and the major pelvic ganglion after intracavernosal penile injection using the rat as an animal model. The results indicated that injection of fluoro-gold (FG) at the penis induces cell body labeling of neurons at the major pelvic ganglion at 2 and 3 days after the injection. Under fluorescent light, the penile injection of FG before pelvic surgery might help to identify the neurovascular bundles, and therefore, preserve potency after radical prostatectomy, for instances. We hope that it could be transposed to clinical setting soon.

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Oestrogen receptors and their relation to neural receptive tissue of the labia minora

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BJU Int. 2008; 101: 1401-6

Objective: To assess the cellular distributions of oestrogen receptors alpha and beta (ER alpha and ER beta) and neuronal nitric oxide synthase (nNOS) in the labia minora, as knowledge about ER type and function may clarify the role of oestrogens in vaginal scar formation and improve outcomes in female genital surgery.
Subjects and Methods: Labial samples were taken from 10 girls (aged 2-9 years) who underwent surgery for labial fusion. The waste tissue strips obtained were used for immunohistochemical identification of ER alpha and ER beta, and nNOS in the labia minora.
Results: There was ER alpha nuclear staining in the stroma of the labia minora close to the clitoris, and basal and suprabasal in the epidermal cells membrane restricted to superficial sections of the labia minora. ER beta was found in the stroma of the labia minora closer to the clitoris and in superficial sections, in the basal epider-

mal cells membrane and apocrine glandular epithelial cells membrane. There was also ER beta cell membrane staining in the basal and suprabasal epithelial cells and fibroblasts in the lamina propria.
Conclusions: Established ER presence allows the consideration of the introitus of the vagina as a target for oestrogen therapy in various clinical and surgical situations. Continuing elucidation of the immunohistochemistry of this external genital tissue might assist in the development of molecular tools to treat genital abnormalities. Details of this immunohistochemistry may also advance the understanding of the effects of sexual differentiation on the brain and other organ systems.

Editorial Comment

These interesting findings confirm our believe that labia minora and other vulvar tissues are estrogen target structures. It is our practice to administer local estrogen for treating labia minora fusion and other vulvar diseases in pre-pubertal, pre-menopausal and post-menopausal women. Also, the present data enable us to expect a greater estrogen effect when administered vaginally, compared with extravaginal administration, as the authors stated. These findings are of clinical importance in the pathophysiology of age-associated and hormonally associated female genital disorders that include both functional and structural changes.

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RECONSTRUCTIVE UROLOGY

Open surgical repair of ureteral strictures and fistulas following radical cystectomy and urinary diversion

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J Urol. 2008; 179: 1428-31

Purpose: Open surgery after cystectomy can be a challenge. We report the incidence of postoperative urinary diversion-enteric fistula and ureteral strictures in patients undergoing radical cystectomy, and discuss the diagnosis and management of these complications, including our surgical approach to these patients.
Materials and Methods: We preformed a retrospective review of 553 patients undergoing radical cystectomy and urinary diversion for bladder cancer between April 1999 and January 2007. Patients in whom a ureteral stricture or fistula developed were identified by serial laboratory and imaging evaluations. A chart review was preformed to identify symptoms, time to stricture or fistula development, radiological findings, type of diversion, estimated blood loss and whether the original anastomosis was stented. Management and outcomes were assessed.
Results: Of 553 patients reviewed ureteral stricture developed in 41 (7.4%) with a mean followup of 20.2 months (range 1 to 98). Strictures developed in 11% (31 of 272) of the orthotopic ileal neobladder, 2.5% (6 of 236) of ileal conduit and 8% (4 of 45) of Indiana pouch cases. Open repair led to an overall success rate of 87%. Urinary diversion-enteric fistula developed in 12 (2.2%) of the 553 patients with a mean followup of 28.4 months (range 3 to 94), all of whom had undergone orthotopic neobladder diversion. No patient had recurrence after surgical repair of the fistula.

Conclusions: Open revision remains the gold standard management for ureteral strictures and urinary diversion-enteric fistulas occurring after radical cystectomy. The addition of the chimney modification to the orthotopic neobladder facilitates surgical repair.

Editorial Comment

Distal and anastomosis uretral strictures occurring after a cystectomy, following a myriad of diversion techniques, is not uncommon. Most likely these problems should be performed primarily in the old fashion way, that is open. In the hands of an experienced endoscopic surgeon the endoureterotomy using a laser can reach a 25% success rate in selected cases as Msezane et al. demonstrated in their retrospective analyzed data.

Sometimes the blood parameters are less sensitive than the follow-up using ultrasound for the upper urinary tract; therefore, we perform both (1). Similar to the presented data we saw the incidence of strictures in ureters in different types of diversion. In addition to those who underwent previous radiation, the placing of an 8F double-J intra-operative might help to reduce the implantation stenoses further (2). Early surgery in our clinic usually involves the re-implantation of both ureters at the same time which we believe helps to avoid further complications. The occurrence of fistulas as reported is a rare case but might be handled with tissue glue if the fistula is small enough before an open surgery is performed (3). The possibilities are more extensive for the majority of cases, however, in the case of urinary diversions, we should be ready to perform open surgery for both cases - strictures and fistulas.

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Randomized comparative study between buccal mucosal and acellular bladder matrix grafts in complex anterior urethral strictures

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J Urol. 2008; 179: 1432-6

Purpose: Urethral strictures have been a reconstructive dilemma for many years due to the limited availability of tissue substitutes and incidence of recurrence. Buccal mucosal grafts have been a favored material in instances where penile skin is unavailable due to its durability and excellent graft survival. Recently collagen based matrices derived from the bladder have been used successfully in patients with stricture disease and hypospadias.

We performed a randomized comparative study to assess the outcome of the acellular bladder matrix compared to buccal mucosa in patients with complex urethral strictures.
Materials and Methods: Human demineralized bone matrix, obtained from cadaveric donors, was processed and prepared for use as an off-the-shelf material. Thirty patients with stricture 21 to 59 years old (mean 36.2) were enrolled and assessed using a standard protocol. The stricture length ranged from 2 to 18 cm (mean 6.9), of which 11 patients had bulbar, 7 had pendulous and 12 had combined bulbo-pendulous strictures. Of the 30 patients, 7 had received no previous intervention while the remaining 23 had undergone 1 to 7 procedures (mean 1.9). All patients were randomized and alternatively assigned to receive either buccal mucosa or demineralized bone matrix and underwent an onlay procedure.
Results: All patients except 2 who were lost during followup were followed for 18 to 36 months (mean 25). In patients with a healthy urethral bed (less than 2 prior operations), the success rate of buccal mucosa grafts (10 of 10) was similar to the bladder matrix grafts (8 of 9) in terms of patency. In patients with an unhealthy urethral bed (more than 2 prior operations), only 2 of 6 patients with a bladder matrix graft were successful, whereas all 5 patients with a buccal mucosa graft had a patent urethra. Postoperative uroflowmetry showed significant voiding improvement in both groups. Histology of the graft biopsies showed normal urethral tissue characteristics.
Conclusions: This study demonstrates that the use of acellular bladder matrix is a viable option for urethral repair. Demineralized bone matrix as an off-the-shelf biomaterial achieves the best results in patients with a healthy urethral bed, no spongio-fibrosis and good urethral mucosa.

Editorial Comment

In recent publications, we have seen the reporting of various off-shelf materials for urethral reconstruction (1,2). Different to the previous publications, the authors compared their shelf material “acellular bladder matrix” against the golden standard of the buccal mucosa graft.

As we all know in the almost virgin wound bed, the first approach always seems to work--if performed correctly. Therefore we should all keep in mind that the first approach might be the most important in order to have a good outcome in the long term (3). In those cases where more than two previous surgeries were performed, the best material still seems to be the buccal mucosa. From this well-designed study, we can learn that as long as we do not have the perfect matrix, we can use one off-shelf in the first run thereby avoiding the additional surgeries needed to harvest buccal mucosa with a similar outcome within a follow-up of mean two years. With the patient we have to make the decision if they are already ready to use this material in the first or second approach (4).

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UROLOGICAL ONCOLOGY

Perineal salvage prostatectomy for radiation resistant prostate cancer

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Eur Urol. 2007; 51: 1565-71; discussion 1572

Objectives: No data are available on the use of perineal prostatectomy for salvage treatment of local recurrent prostate cancer after radiotherapy. Here we report on the clinical aspects and follow-up of salvage perineal prostatectomy.
Materials and Methods: Twenty-seven patients underwent a perineal salvage prostatectomy from 1997-2005 for biopsy-proven local recurrent prostate cancer after external beam (n = 22) or brachyradiotherapy (n = 5). Staging included physical examination, prostate-specific antigen (PSA), transrectal ultrasound, computed tomography scan, and bone scan.
Results: Mean PSA before surgery was 8.6 ng/mL (± 2.8 ng/mL). Comparing clinical staging with final pathologic staging after salvage perineal prostatectomy showed a 67% clinical understaging. Mean blood loss was 677 cc, and perioperative morbidity consisted of prolonged anastomotic leakage (n = 8), urosepsis (n = 3), prolonged hematuria (n = 3), urinary retention (n = 2), and rectal perforation (n = 1). One patient died during the postoperative course because of urosepsis and endocarditis. At an interval of at least 12 mo after surgery, 37% (10 of 27) and 7% (2 of 27) of patients reported normal continence and erectile function, respectively. Five patients died during a mean follow-up of 43 mo; two patients died of prostate cancer. Five-year biochemical recurrence-free survival was 31% (95% CI, 25-42%). In a multivariate Cox regression analysis the serum PSA and PSA doubling time (PSADT) at the time of surgery were the best predictors of biochemical recurrence-free survival. No patient with a PSA > 2 ng/mL and a PSADT < 12 mo was without biochemical recurrence 2 yr after surgery.
Conclusions: Salvage perineal prostatectomy showed functional results that favorably compare with the retropubic approach, but considerable morbidity is still frequent. Proper patient selection therefore is mandatory. A serum PSA level of > 2 ng/mL and PSADT < 12 mo independently predict shorter biochemical recurrence-free survival.

Editorial Comment

Data on salvage prostatectomy after previous radiotherapy are sparse. This report focuses on perineal prostatectomy in this patient group. Several interesting features in this report are worthwhile reporting and considering in patients with a similar situation.
First, understaging is a major event. Fifty-eight percent of patients had positive surgical margins. This translates into low long-term cure rates that are given in Figure-1 of the manuscript. After 5 years, only 20% of patients still were free of PSA recurrence. Of further importance is the fact that only patients with a preoperative PSA of < 2 ng/mL remained free of biochemical recurrence.

In fact, radical salvage prostatectomy remains a procedure that should be elected in few highly elected patients.

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A prospective randomized EORTC intergroup phase 3 study comparing the complications of elective nephron-sparing surgery and radical nephrectomy for low-stage renal cell carcinoma

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Eur Urol. 2007; 51: 1606-15

Objectives: This study compared the complications and the cancer control of elective nephron-sparing surgery (NSS) and radical nephrectomy (RN) in patients with a small (< or = 5 cm), solitary, low-stage N0 M0 tumour suspicious for renal cell carcinoma (RCC) and a normal contralateral kidney.
Methods: 541 patients were randomised in a prospective, multicentre, phase 3 trial to undergo NSS (n = 268) or RN (n = 273) together with a limited lymph node dissection.
Results: This publication reports only on the complications reported for both surgical methods. The rate of perioperative blood loss < 0.5l was slightly higher after RN (96.0% vs. 87.2%) and the rate of severe haemorrhage was slightly higher after NSS (3.1% vs. 1.2%). Ten patients (4.4%), all of whom were treated with NSS, developed urinary fistulas. Pleural damage (11.5% for NSS vs. 9.3% for RN) and spleen damage (0.4% for NSS and 0.4% for RN) were observed with similar rates in both groups. Postoperative computed tomography scanning abnormalities were seen in 5.8% of NSS and 2.0% of RN patients. Reoperation for complications was necessary in 4.4% of NSS and 2.4% of RN patients.
Conclusions: NSS for small, easily resectable, incidentally discovered RCC in the presence of a normal contralateral kidney can be performed safely with slightly higher complication rates than after RN. The oncologic results are eagerly awaited to confirm that NSS is an acceptable approach for small asymptomatic RCC.

Editorial Comment

This is the first report of a large randomized phase III trial on renal-sparing surgery (RSS) versus radical nephrectomy (RN) in patients with renal cancer. The trial is large enough to give meaningful results and therefore will be a standard reference in the future. In this paper, only the results of complications that have occurred are given whereas the results on oncological outcome have still to be awaited.

In this trial, only tumors smaller than 5 cm were considered eligible for RSS as, to my opinion, the rate of complications would increase sharply in larger tumors. In this way, RSS was a safe procedure. Still, a higher complication rate (which in fact was doubled in RSS patients) was detectable with a rate of severe hemorrhage of 3.1% in RSS vs. 1.2% in RN and the occurrence of urinary fistulas in 4.4% in RSS.

With these results in mind, we have to await the long-term data on oncological outcomes. As of now, renal-sparing surgery seems a safe procedure in elective patients with tumors < 5 cm.

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NEUROUROLOGY & FEMALE UROLOGY

The evolution of obstruction induced overactive bladder symptoms following urethrolysis for female bladder outlet obstruction

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Purpose: Bladder outlet obstruction following stress incontinence surgery may present as a spectrum of lower urinary tract symptoms. We evaluated the prevalence and impact of persistent overactive bladder symptoms following urethrolysis for iatrogenic bladder outlet obstruction.
Materials and Methods: In a retrospective review we identified 40 patients who underwent urethrolysis. All patients underwent a standardized urological evaluation. Patients identified with genitourinary erosion, neurogenic bladder dysfunction and preexisting overactive bladder were excluded. Urethrolysis outcomes were determined by subjective bladder symptoms and objective parameters. Validated questionnaires were completed to assess symptom bother, patient satisfaction and quality of life. Statistical analyses were performed using Stata, version 9.0.
Results: A total of 40 patients were included in the study with a mean ± SD followup of 13 ± 11 months (range 3 to 38). Of the patients 34 patients presented with obstructive symptoms, while 36 had overactive bladder symptoms. Obstructive symptoms resolved in 28 of the 34 patients (82%), while overactive bladder symptoms resolved completely in only 12 (35%) and they were significantly improved in 4 (12%). Overall 20 patients (56%) were on antimuscarinics for refractory overactive bladder and 8 ultimately required sacral neuromodulation. Pre-urethrolysis detrusor overactivity was more likely in patients with persistent overactive bladder symptoms than in those in whom overactive bladder symptoms resolved (70% vs. 38%). Patients with persistent overactive bladder had significantly greater symptom severity/bother, and decreased perception of improvement and quality of life following urethrolysis.
Conclusions: Following urethrolysis overactive bladder symptoms may remain refractory in 50% or greater of patients, which has a negative impact on quality of life and the impression of improvement after surgery. Detrusor overactivity demonstrated preoperatively may be useful for predicting who may have persistent overactive bladder symptoms despite an effective urethrolysis procedure.

Editorial Comment

This report highlights the difficulties of achieving normal voiding function after urethrolysis for iatrogenic female bladder outlet obstruction. The authors were able to review 40 patients who underwent a variety of urethrolysis techniques and categorized their operative success on whether the symptoms were primarily obstructive or overactive bladder in nature. The authors noted that it was much easier to resolve obstructive voiding symptoms than those of overactive bladder. The surgical success rate for symptoms of bladder overactivity was under 50 percent; in addition, 20 percent of their overall patients (8/40) eventually needed metachronous sacral nerve stimulation.

A very well written article that clearly highlights the difficulties in the management of this patient population. Simply addressing the obstructing operation unfortunately will not return the patient to normal voiding function. It is notable that none of the patients in the group appear to have had an obstructing transobturator sling (timing of the original surgery?). The authors highlight that identification preoperatively of detrusor overactivity may be a negative predictor of patient perceived success after their urethrolysis.

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Botulinum A toxin intravesical injection in patients with painful bladder syndrome: 1-year followup

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Purpose: We evaluated the 1-year efficacy and tolerability of botulinum A toxin intravesically injected in patients with painful bladder symptoms associated with increased urinary frequency, refractory to conventional treatments.
Materials and Methods: Three men and 12 women were prospectively included in the study. Under short general anesthesia the patients were given injections of 200 U commercially available botulinum A toxin diluted in 20 ml 0.9% NaCl. Injections were performed submucosally in the bladder trigone and lateral walls under cystoscopic guidance. A voiding chart and the visual analog scale for pain were used, and urodynamics were performed before treatment, and 1, 3, 5 and 12 months later.
Results: Overall 13 patients (86.6%) reported subjective improvement at the 1 and 3-month followups. The mean visual analog scale score, and daytime and nighttime urinary frequency were significantly decreased ($p < 0.05$, < 0.01 and < 0.05, respectively). At the 5-month followup the beneficial effects persisted in 26.6% of cases but increased daytime and nighttime urinary frequency, and an increased visual analog scale score were observed compared to baseline. At 12 months after treatment pain recurred in all patients. Nine patients complained of dysuria 1 month after treatment. Dysuria persisted in 4 cases at the 3-month follow-up and in 2 at the 5-month follow-up. Conclusions: Intravesically injected botulinum toxin A is effective for short-term management of refractory painful bladder syndrome. The beneficial effects decreased progressively within a few months after treatment. Thus, repeat injections of the neurotoxin are required for efficacious treatment in patients with the disease.

Editorial Comment

The authors review their experience with Botulinum A toxin intravesical injection in patients plagued with refractory bladder pain combined with symptoms of overactive bladder (frequency, urgency, nocturia). The study noted a definitely subjective improvement at one to three months post therapy but by one year post injection, the patients had returned to their baseline. The therapy was basically well tolerated but there was a substantial number of patients (9/13) that had dysuria in addition to 20 percent of the patients needing a period of self intermittent catheterization post procedure.

The report helps highlight the exciting use of Botulinum A toxin in urology. Though no medication is a panacea, it appears that the use of this intravesical agent may assist the urologist in treating a segment of our patient population that is among the most challenging. This report raises the question that patients with a non neurogenic type of voiding dysfunction may have a higher rate of urinary retention secondary to the Botulinum A toxin. Given this finding, it will be worthwhile for the treating physician to alert the patient that self intermittent catheterization is a distinct potential reality after this therapy. Unfortunately, even with a good response, patients will require repeat therapy to continue the beneficial effect; as noted in this paper the patients did request repeat a treatment because of the symptomatic relief they enjoyed. Given that there is a high rate of placebo effect in this patient population, enthusiasm should be tempered until a placebo controlled randomized study may be completed.

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PEDIATRIC UROLOGY

Antibiotic prophylaxis for the prevention of recurrent urinary tract infection in children with low grade vesicoureteral reflux: results from a prospective randomized study

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Purpose: Antibiotic prophylaxis is given to children at risk for urinary tract infection. However, evidence concerning its effectiveness in grade I to III vesicoureteral reflux is lacking. The objective of this study was to determine whether antibiotic prophylaxis reduces the incidence of urinary tract infection in young children with low grade vesicoureteral reflux.

Materials and Methods: Children 1 month to 3 years old with grade I to III vesicoureteral reflux were assigned randomly to receive daily cotrimoxazole or no treatment, and followed for 18 months. A urinary tract infection constituted an exit criterion. Infection-free survival rates were calculated using the Kaplan-Meier method and compared using the log rank test.

Results: A total of 225 children were enrolled in the study. Distribution of gender, age at inclusion and reflux grade were similar between the 2 groups. There was no significant difference in the occurrence of urinary tract infection between the 2 groups (17% vs. 26%, $p = 0.2$). However, a significant association was found between treatment and patient gender ($p = 0.017$). Prophylaxis significantly reduced urinary tract infection in boys ($p = 0.013$), most notably in boys with grade III vesicoureteral reflux ($p = 0.042$).

Conclusions: These data suggest that antibiotic prophylaxis does not reduce the overall incidence of urinary tract infection in children with low grade vesicoureteral reflux. However, such a strategy may prevent further urinary tract infection in boys with grade III reflux.

Editorial Comment

This study again tries to demonstrate whether prophylactic antibiotics are of value in refluxing patients and could not show a significant difference for prophylaxis in mild refluxing patients, except in Grade III boys.

I have concerns with urine samples of bag collections and their lack of attempt to define poor compliance. Previous studies have either measured drug excretion in the urine or sensitivity of the bacteria to the antibiotic that the patient was taking and 27% of the E-coli infections in the prophylactic group were sensitive to the medication that the patient was supposed to be taking. Other studies have suggested up to one-third of patients and parents are non-compliant with recommended prophylactic treatments.

I must admit that I do struggle with data such as this, where 17% of the treatment patients had an infection and 26% of the no treatment had an infection. This brings into question the difference between statistical significance and clinical significance, and makes it hard to recommend no treatment over prophylactic antibiotics. It points out how difficult it is to do a large study with sufficient number of patients to leave the readers without any doubt of the proper treatment. It is tempting to make the conclusion that no treatment is the right answer but I wonder whether the more cautious approach is to recommend early surgical treatment of reflux, which has been shown to protect kidneys from scarring, even though it does not alter the recurrent UTI rate.

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Failed pyeloplasty in children: comparative analysis of retrograde endopyelotomy versus redo pyeloplasty

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Purpose: We compared retrograde endopyelotomy to redo pyeloplasty for the treatment of failed pyeloplasty in children.
Materials and Methods: Of 32 patients with recurrent ureteropelvic junction obstruction retrograde endopyelotomy was performed in 18 and redo pyeloplasty was performed in 14. Patient age, gender, side, stent placement at initial pyeloplasty, presentation of secondary ureteropelvic junction obstruction, hospital stay, complications and success rates were compared. Success was defined as radiographic relief of obstruction as determined by ultrasound or diuretic renography at latest followup.
Results: Median patient age was 6 years (range 2 to 14) at retrograde endopyelotomy and 7.2 years (1 to 17) at redo pyeloplasty. Retrograde endopyelotomy technique consisted of holmium laser in 10 patients and cautery/balloon dilation in 8. Redo pyeloplasty was performed through a flank incision in 12 patients and by laparoscopy in 2. Retrograde endopyelotomy was successful in 39% of the patients, while redo pyeloplasty had a 100% success rate ($p = 0.002$). Of the patients with failed retrograde endopyelotomy 5 had a stricture greater than 1 cm and 7 were younger than 4 years. Mean length of the narrowed ureteral segment was 10.1 mm in the failed retrograde endopyelotomy group vs. 5.8 mm in the successful group ($p < 0.01$). Only 1 of 8 children (13%) had a successful retrograde endopyelotomy using cautery followed by balloon dilation. Hospital stay was 1.3 days for the retrograde endopyelotomy group and 2.9 days for the redo pyeloplasty group ($p < 0.01$). Mean followup was 47 months (range 15 to 132) after retrograde endopyelotomy and 33.1 months (12 to 78) after redo pyeloplasty.
Conclusions: Retrograde endopyelotomy had a significantly lower success rate than redo pyeloplasty for correction of recurrent ureteropelvic junction obstruction after failed pyeloplasty in children. Patient age less than 4 years and narrowed ureteral segment greater than 10 mm were associated with a poor outcome after retrograde endopyelotomy.

Editorial Comment

Redo pyeloplasty was remarkably successful with an average of a 3 day stay in the hospital. One wonders about patient selection in a study such as this, as obviously that could make a great difference in the outcome.

These authors suggested that patients under 4 and strictures longer than a centimeter were not as well treated with endoscopic techniques. An interesting thought suggested by the authors was that patients, who did not have an initial ureteral stent and then subsequently had failure, perhaps had more urine leakage and fibrosis and were better treated by redo pyeloplasty than endoscopic techniques. The authors did not comment on whether the endoscopic techniques made redo pyeloplasty afterwards any more difficult but all their open pyeloplasties were successful after their endoscopic procedures. This is a difficult segment of patients to deal with and all of the urologic techniques should be considered. In these authors' hands, the retrograde endopyelotomy with electrocautery was not very successful.

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