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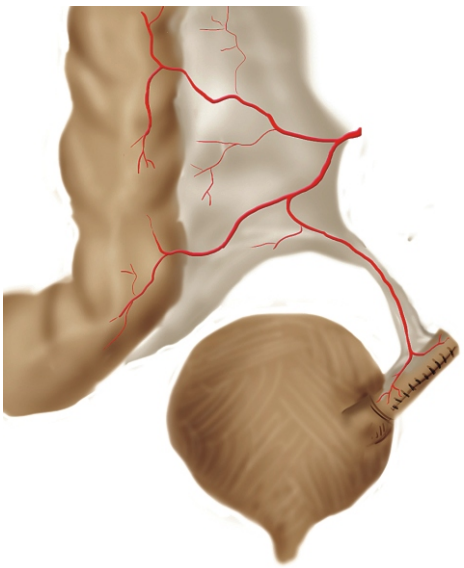

Anastomosis of newly build tube on postero-lateral bladder. (Page 317)

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EDITOR'S COMMENT

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Undergrading and Understaging in Prostate Cancer

The May - June 2010 issue of the International Braz J Urol presents original contributions and editorials from many different countries, such as USA, Germany, France, Greece, Canada, Brazil, Spain, Italy, Korea, Iran, Belgium, England, etc., and as usual, the editor's comment highlights some papers.

Doctor Oliveira and co-workers, from University of Sao Paulo, Brazil, evaluated on page 292 the undergrading and understaging rates in patients with clinically localized insignificant prostate cancer who underwent radical prostatectomy. Ninety-three patients fulfilled their criteria of non-significance: Gleason score < 7, stage T1c, PSA < 10 ng/mL and percentage of affected fragments less than 25%. The pathologic stage and Gleason score were compared to preoperative data to evaluate the rate of understaging and undergrading. The biochemical recurrence free survival of these operated insignificant cancers were also evaluated. They found on surgical specimen analysis that 74.7% of patients had Gleason score of 6 or less and 25.3% had Gleason 7 or greater. Furthermore, 8.3% of cases showed extracapsular extension. After 36 months of follow-up 3.4% had biochemical recurrence, defined by a PSA above 0.4 ng/mL. As conclusion, the authors have found considerable rates of undergrading and understaging in patients with prostate cancer whose current definitions classified them as candidates for active surveillance. Three of the most active urological pathologists in the world provided important editorial comment on this paper.

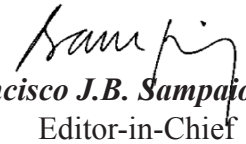
Doctors Yang and Flaig, from University of Colorado Denver School of Medicine, Colorado, USA, presented on page 273 a nice review on novel targeted agents for the treatment of bladder cancer and discussed the translating laboratory advances into clinical application. The high frequency of recurrence of noninvasive bladder cancer and poor survival rate of invasive bladder cancer emphasizes the need for novel therapeutic approaches. The mechanisms of tumor development and promotion in bladder cancer are strongly associated with several growth factor pathways including the fibroblast, epidermal, and the vascular endothelial growth factor pathways. In this review, efforts to translate the growing body of basic science research of novel treatments into clinical applications were explored.

Doctor Kariotis and co-workers, from "Asklipieion" General Hospital, Athens, Greece, determined on page 308 whether the peri-procedural administration of low-dose aspirin increases the risk of bleeding complications for patients undergoing extended prostate biopsies. They studied 530 men undergoing extended needle biopsies divided into two groups: those receiving aspirin and

those not receiving aspirin. The authors found no significant differences between the two groups regarding the mean number of biopsy cores. No major biopsy-related complications were noted. Statistical analysis did not demonstrate significant differences in the rate of hematuria, rectal bleeding or hemospermia. The mean duration of hematuria and rectal bleeding was significantly greater in the aspirin group compared to the control group. A multivariate logistic regression analysis revealed that only younger patients (mean age 60.1 ± 5.8 years) with a lower body mass index (< 25 kg/m2) receiving aspirin were at a higher risk for developing hematuria and rectal bleeding after the procedure. It was concluded that the continuing use of low-dose aspirin in patients undergoing extended prostatic biopsy is a relatively safe option since it does not increase the morbidity of the procedure.

Doctor Hosseini and collaborators from Shaheed Beheshti Medical Sciences University, Tehran, Iran, reported on page 317 their experience with Monti's channel urinary diversion on the management of patients with long urethral defect with history of one or more failed urethroplasties. After Monti's procedure, all eight patients studied performed catheterization through the conduit without difficulty and stomal stenosis. There was no dehiscence, necrosis or perforation of the tube. The authors concluded that Monti's procedure seems to be a valuable technique in patients with very long complicated urethral defect who cannot be managed with routine urethroplasty techniques. Dr. Monti, from Federal University of Minas Triangle, Brazil, Dr. Lumen, from Ghent University Hospital, Belgium, Dr. Lazzeri, from Santa Chiara Hospital and Dr. Barbagli from Arezzo, Italy, provided important editorial comments on this article.

Finally, it is my great pleasure to register that our peer-review Video Section, under the leadership of Dr. Philippe Spiess from Moffit Cancer Center, FL, USA, is a great success and is receiving more and more submissions. After submission, the videos are reviewed by members of the specific board or ad-hoc reviewers and if accepted they are placed in the Video Library at the Journal's site. Also, an Abstract of the video with an Editorial Comment provided by one of members of the board is published in the corresponding issue of the Journal.



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

Review Article

International Braz J Urol

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Techniques of Nerve-Sparing and Potency Outcomes Following Robot-Assisted Laparoscopic Prostatectomy

Sanket Chauhan, Rafael F. Coelho, Bernardo Rocco, Kenneth J. Palmer, Marcelo A. Orvieto, Vipul R. Patel

Global Robotics Institute (SC, RFC, BR, KJP, MAO, VRP), Florida Hospital - Celebration Health, Department of Urology, University of Central Florida School of Medicine, Celebration, Florida, USA, Division of Urology (RFC), University of Sao Paulo, SP, Brazil and Division of Urology, European Institute of Oncology, Milan, Italy

ABSTRACT

Purpose: Nerve sparing radical prostatectomy is the gold standard for the treatment of prostate cancer. Over the past decade, more and more surgeons and patients are opting for a robot-assisted procedure. The purpose of this paper is to briefly review different techniques and outcomes of nerve sparing robot assisted laparoscopic prostatectomy (RALP).
Materials and Methods: We performed a MEDLINE search from 2001 to 2009 using the keywords "robotic prostatectomy", "cavernosal nerve", "pelvic neuroanatomy", "potency", "outcomes" and "comparison". Extended search was also performed using the references from these articles.
Results: Several techniques of nerve sparing are available in literature for RALP, which have been described in this manuscript. These include, "the veil of Aphrodite", "athermal retrograde neurovascular release", "clipless antegrade nerve sparing" and "clipless cautery free technique". The comparative and the non comparative series showing outcomes of RALP have been described in the manuscript.
Conclusions: The basic principles for nerve sparing revolve around minimal traction, athermal dissection, and approaching the correct planes. It has not been documented if any one technique is better than the other. Regardless of technique, patient selection, wise clinical judgment and a careful dissection are the keys to achieve optimal oncological outcomes following RALP.

Key words: *prostatic neoplasm; prostatectomy; robotics; outcomes*
Int Braz J Urol. 2010; 36: 259-72

INTRODUCTION

Prostate cancer is the most commonly diagnosed cancer among men in United States. According to a recent estimate, 192,280 (25%) new patients will be diagnosed with prostate cancer in the year 2009, making it the most commonly diagnosed cancer in men and the second most common cause of death in men (1). Retropubic Radical Prostatectomy (RRP) is still the gold standard for the treatment of organ confined prostate cancer, offering better survival rates, when compared to conservative management (2). With the advances in Minimally Invasive Surgery (MIS) and its application to the Urology field, Schuessler et al. performed the first Laparoscopic Radical Prostatectomy (LRP) in 1992 (3). However, the procedure was associated with a long learning curve related to the reduced range of motion, loss of

3D vision, counter-intuitive hand eye coordination, poor surgeon ergonomics and loss of tactile feedback. The recent introduction of advanced robotic devices such as the da Vinci Surgical System (Intuitive Surgical, Inc., Sunnyvale, CA) to the field of urologic surgery has added new hopes of reducing operative times and the learning curve for minimally invasive prostatectomy. Binder and Kramer (4) performed the first Robot Assisted Laparoscopic Prostatectomy. (RALP) in 2000 and since then, it has become an increasingly popular treatment option. The technique for this procedure has been described earlier (5) However, it is controversial whether RALP has any specific advantage over open or laparoscopic procedures. Some studies suggest that RALP has clear advantage over conventional procedures even in during the learning curve, (6) while others show no such advantage (7).

Postoperative potency and continence rates are used as surrogates to mark the functional efficacy of this procedure. However, it is still extremely difficult to precisely predict the outcomes after radical prostatectomies . The potency rates, particularly, depend on many factors such as pre-operative erectile function, patient co-morbidities, type and extent of nerve sparing, patient's age, frequency of intercourse, use of medications and the experience of the surgeon (8). This list is not exclusive and there is no foolproof "formula" to ascertain potency recovery even in younger patients.

Many technical refinements and approaches to nerve sparing during RALP have been described in recent years aiming to improve the potency outcomes after surgery. In this review we discuss these techniques and present the potency outcomes after RALP currently available in medical literature.

MATERIALS AND METHODS

A MEDLINE search was performed between 2000 and 2009 using the keywords "robotic prostatectomy", "nerve sparing", "cavernosal nerve", "pelvic neuroanatomy", "potency", "outcomes" and "comparison". We performed additional hand searches based on references from relevant review articles (9-11). Studies published only as abstracts and reports from meetings were not included in the review. Only studies published in English language were included. Comparative and non-comparative studies were included. Outcomes were tabulated and analyzed from the resulting articles.

BASIC ANATOMICAL PRINCIPLES FOR NERVE SPARING PROCEDURES

The first mention of neural structures having a role in potency was made as early as 1863 when Eckhard defined nervi erigentus in animal models (12). More than one century later, Walsh in a series of studies described the detailed anatomy of cavernous nerves and its importance in preserving the potency after radical prostatectomy. After tracing the autonomic innervation of the corpora cavernosa in a male fetus and newborn, Walsh and Donker (13) demonstrated that branches of the pelvic plexus that innervate the corpora cavernosa are situated between the rectum and urethra, and penetrate the urogenital diaphragm near or in the muscular wall of the urethra. The neuro-vascular bundle of Walsh (syn: cavernosal nerve, bundle of Walsh or most commonly, just NVB) is a tubular structure that runs dorso-laterally to the prostate as an inferior extension to the pelvic plexus (syn: inferior hypogastric plexus, pelvic ganglion). Based on these findings, he proposed an anatomical concept and modifications for radical prostatectomy (14) where the lateral pelvic fascia was incised anterior to the NVBs, and the lateral pedicle is divided close to the prostate to avoid injury to the branches of the pelvic plexus that accompany capsular vessels of the prostate. This marked a new era in the treatment of prostate cancer where the benefits outweighed the risks for the then highly invasive procedure of radical prostatectomy. Walsh later verified these findings in a 60 year old human cadaver (15).

In 2004, Costello and colleagues (9) demonstrated in their human cadaver studies that most of the NVB descends distally and dorso-laterally to seminal vesicles (posterior nerves), while anterior nerves course along the posterior-lateral border of seminal vesicles (Figure-1). The anterior and posterior nerves of NVB are separated by a distance of 3 cm at the base of prostate. These run distally towards the apex, converge at mid prostatic level, and then diverge

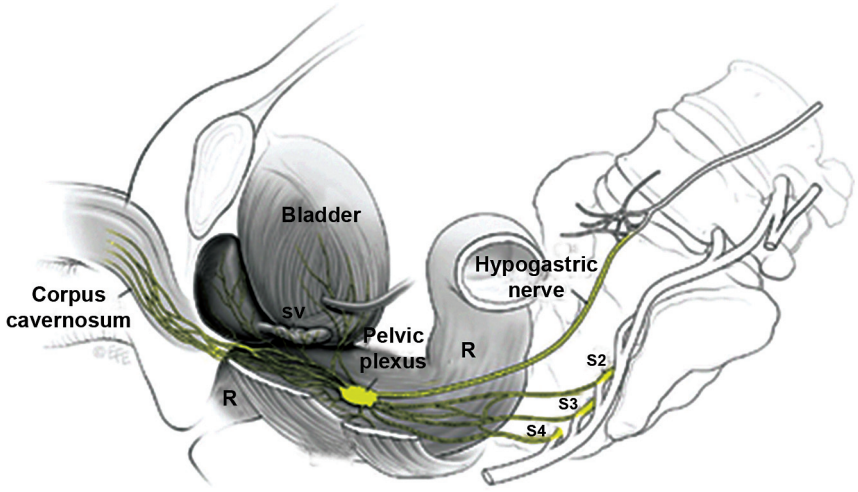

Figure 1 *– The pelvic plexus and formation of neurovascular bundles, reprinted from Costello et al. (9) (with permission from Wiley-Blackwell Publishing).*

again as they approach the prostate apex, where it is most variable in course and architecture.

In 2006, Tewari et al. (10) demonstrated in their study on 10 fresh and 2 fixed male cadavers, a tri-zonal neural architecture relevant to robotic prostatectomies. They described the presence of a proximal neurovascular plate (PNP), a predominant neurovascular bundle (PNB) and accessory neural pathways (ANPs). The PNP include vesical and prostatic subdivision of the pelvic plexus and was composed of ganglia and interconnecting nerve fibers which process and relay erectogenic neural signals. The PNB is the classical nerve bundle that carries neural impulses to the cavernosal tissue. It is contained between the layers of lateral pelvic and/or levator fascia, and is postero-lateral to the prostate. The ANPs are putative accessory pathways usually within the layers of lateral pelvic fascia and/or levator fascia and lies posterolateral or anterolateral to the prostate.

The Fascial Planes for Nerve Sparing

To prevent mechanical and thermal injury during dissection of the NVB, the appropriate plane needs to be developed based on its anatomical relationship with the periprostatic fascial planes. To understand these planes, the knowledge of the anatomy of pelvic fascial structures is necessary. The high magnification offered on a robotic platform enables the surgeon to accurately identify the surgical landmarks and to create and enter the plane of interest. Ayala et al. reviewed 50 specimens from radical prostatectomy for prostate cancer and reported that prostate capsule is not a true capsule but a fibro-muscular band located between glandular units and peri-prostatic connective tissue (11). The endopelvic fascia is a multilayer fascia that covers the prostate and the bladder and is linked to the prostate capsule by collagen fibers, finally inserting in the form of puboprostatic ligaments to the pubic bone. The part of endopelvic fascia that covers the prostate is called the prostatic fascia. The outer part of endopelvic fascia is called Levator fascia or Lateral Pelvic fascia. Denonvilliers fascia is the fascia that covers the rectum posterior to the prostate. Martínez-Piñeiro et al. (16) describe an anterior extension to Denonvilliers fascia which fuses laterally with the endopelvic fascia.

An intrafascial plane is the plane between the prostate capsule and the prostatic fascia. Hence, during an intrafascial dissection, the endopelvic fascia is incised only ventrally, medial to the puboprostatic ligaments (17). The interfascial plane is the plane between the prostatic fascia and the lateral pelvic fascia. Posteriorly, the interfascial plane exists as the

avascular plane between the prostatic fascia and the Denonvilliers fascia and between the prostatic fascia and the anterior extension of Denonvilliers fascia. Most of the NVBs lie between the anterior extension of the Denonvilliers fascia and the levator fascia. Hence complete preservation of NVBs is achieved with either intrafascial or interfascial dissection. Dissection along extrafascial plane is right through the NVBs and might enable some preservation of the neural tissue or none (Figure-2).

Significance of Athermal Dissection

It is important to dissect the NVBs without the use of thermal energy because these nerves have unmyelinated structure that makes them vulnerable to the dissipated thermal energy. In their studies on canine models, Ong and associates assessed the erectile function acutely after the surgery and after 2 weeks of survival by measuring peak intracavernous pressures in response to cavernous nerve stimulation (18). The use of monopolar or bipolar sources in the vicinity of the prostate during dissection of the neurovascular bundle was clearly associated with a significantly decreased erectile response to cavernous nerve stimulation.

Subsequently, Ahlering et al. in their case control series demonstrated the effect of thermal energy on the return of sexual activity (19). Potency was defined as "erections hard enough for vaginal penetration with or without the use of PDE-5 inhibitors". In the cautery group, 14.7% of patients were potent after 9 months (UNS-10%; BNS-16.7%) and 63.2% were potent at 24 months (UNS-50%; BNS-67.9%), as compared to 69.8% (UNS-56.3%; BNS-72.8%) and 92% (UNS-83.3%; BNS- 92%) respectively for the cautery free group.

In a recent modification, Ahlering et al. (20) reported hypothermic nerve sparing on 50 consecutive patients. Pelvic cooling was achieved using cold irrigation and an endorectal cooling balloon cycled with 4°C saline. The lubricated balloon was inserted via the anus, and an esophageal probe was used to obtain the

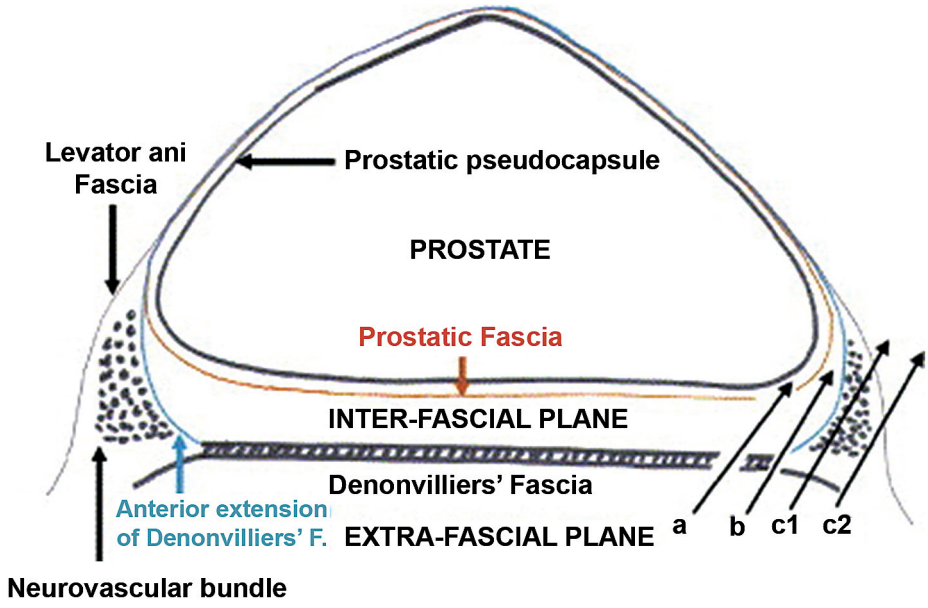

Figure 2 – *Axial view of prostatic fascial anatomy. a = intrafascial plane; b = interfascial plane; c1 = extrafascial plane with partial preservation of neurovascular bundle; c2 = extrafascial plane with no preservation of neurovascular bundle. (9) (with permission from Elsevier publishing).*

intracorporeal temperature readings directly from the surface of anterior rectum/NVBs. This has shown to significantly improve post-operative continence. The potency outcomes are still awaited.

Gianduzzo et al. (21) have recently evaluated cavernous nerve function following KTP laser dissection and compared outcomes to those of ultrasonic shears and cold scissor dissection. Peak intracavernous pressure upon cavernous nerve stimulation was expressed as a percent of mean arterial pressure. This was measured acutely and at 1 month after the surgery on a canine model. Thermal spread from the KTP laser and ultrasonic shears was assessed histologically ex vivo in a harvested peritoneum. The median depth of acute laser injury was 600 μm compared to 1.2 mm for ultrasonic shear dissection and 450 μm crush injury due to the athermal technique. Thermography revealed less collateral thermal spread from the laser than from the ultrasonic shears (median greater than 60ºC thermal spread 1.07 vs. 6.42 mm, $p < 0.01$). Hence KTP laser had similar outcomes as athermal technique and was superior to ultrasonic shears for preserving cavernous nerve function.

TECHNIQUES OF NERVE SPARING AND POTENCY OUTCOMES FOLLOWING RALP

The nerve sparing is an important step in radical prostatectomy that determines the functional outcomes of the procedure. Hence every attempt should be made to preserve the NVBs. The surgical dilemma however is that an ambitious nerve sparing might lead to higher positive surgical margin (PSM) rate. Although some recent studies have shown the feasibility of using Optical Coherence Tomography (OCT) on the pathological specimen and predicting the PSM and Extra capsular Extension (ECE) rate, this technology has not yet diffused into the clinical practice (22). Hence a wise clinical decision should be made before proceeding with the nerve sparing.

The approach to nerve sparing can be from the prostate base to apex (antegrade) or from apex to base (retrograde), unilateral or bilateral, partial or full. These terms are self explanatory. The mechanical trauma to the nerves might also be caused by the method of handling of the pedicles which are essentially a vascular structure, but very closely related to NVBs. These pedicles can be controlled by clamping, clipping or suturing. Several nerve sparing techniques have been described in literature.

The 'Veil of Aphrodite' Technique (Syn: high anterior release, curtain dissection)

Aphrodite was the Greek Goddess of love, beauty and sexual ecstasy. The veil is an area of cavernosal nerves that extends from the posterolateral to the anterolateral surface of the prostate like a curtain (23,24). The avascular interfascial plane between the posterior prostatic fascia and Denonvilliers fascia is extended as distally as possible towards the apex, and laterally to expose pedicles which lie anterior to the pelvic plexus and NVBs. The pedicles are divided by clipping or bipolar cauterization and after appropriate countertractions, the prostatic fascia is incised anteriorly to enter the intrafascial plane. Meticulous sharp and blunt dissection on the fascia is performed athermally until the entire peri-prostatic fascia is released like a veil hanging from the pubo-uretheral ligaments (Figure-3).

In their series published in 2007, Menon et al. selected 1142 out of 2652 patients who underwent RALP at their institute with at least 1 year follow-up. Potency was defined as the ability to have erections adequate enough for vaginal penetration. 70% of patients who were potent before the surgery (SHIM > 21) and had a BNS, were able to achieve sexual intercourse after surgery with or without the use of PDF-5 inhibitors (25).

The veil technique has recently been modified by these authors in an attempt to preserve the pubovesical ligaments and the Dorsal Venous Complex (DVC). The technical modification consists of extending the interfascial dissection anteriorly and intrafascially between 11 o'clock and 1 o'clock position, ("superveil" sparing). Cold scissors or hot monopolar hook is used where the prostatic fascia is adherent to the capsule. In 85 patients who used phosphodiesterase-5 inhibitors, and attempted sexual intercourse, 94% had erections sufficient for penetration on a median follow-up of 18 months (26).

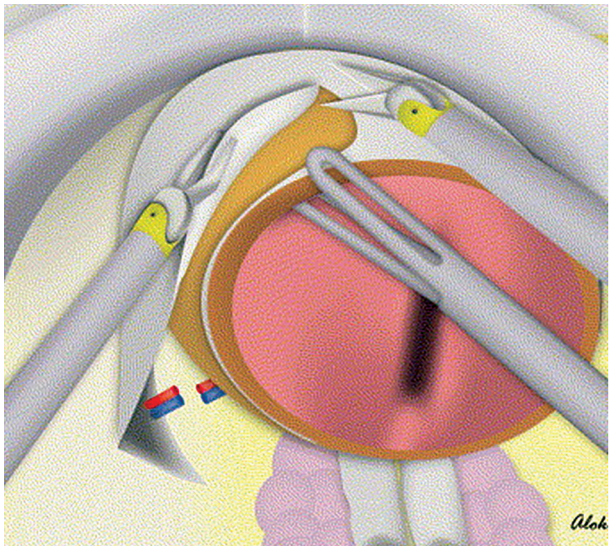

Figure 3 *– Place of dissection for 'veil of Aphrodite' (from ref. 21, with permission from Elsevier publishing).*

Athermal Early Retrograde NVB Release During Antegrade Prostatectomy

The conventional approach to nerve sparing during laparoscopic and robotic prostatectomy has been from the prostate base to apex (antegrade). However, the NVB is closely and complexly related to the base of the prostate, which might be at risk of inadvertent trauma during an antegrade approach to nerve sparing. Based on this philosophy, Patel et al. (27) have reported a unique technique whereby the NVBs are approached in a retrograde fashion (from apex to base). The lateral pelvic fascia is incised at the level of apex and the mid portion of prostate and an avascular plane is developed between the NVBs and the prostatic fascia. This plane is extended posteriorly until it meets the interfascial plane developed initially between the prostate and the rectum. The entire dissection is carried out athermally. The vascular pedicle is ligated with a hemolock clip which is placed above the NVB. Releasing the bundle early and delineating its path avoid inadvertent damage at his point. It is then released distally to the level of pelvic floor to avoid damaging it during the apical dissection or vesico-urethral anastomosis.

These authors published their series of 397 consecutive patients out of which 233 (58.7%) had a BNS and 51 (12.8%) had a UNS using this modified technique. Potency was defined as having erections sufficient enough for vaginal penetrations with or without the use of PDE-5 inhibitors. Patients with preoperative Sexual Health Inventory for Men (SHIM) score higher than 21 who had at least 3 months follow-up (n = 98) showed a potency rate of 87.7% and for the patient group with SHIM between 17 and 21, the potency rate was 73%.

Clipless Antegrade Nerve Sparing

Chien et al. (28) have described clipless antegrade technique for nerve sparing where they use a combination of cold cutting with judicious use of monopole and bipolar energy during this approach. The interfascial plane is created posterior to prostate to release it from its posterior attachments on the rectum. This plane is continued towards the apex along the midline. The vascular pedicles are swept off the prostatic pedicles using a combination of blunt and sharp cold scissors in a medial to lateral dissection. The vascular pedicles are then mobilized in the anterior direction until its distal end where the small vessels that penetrate into the prostate capsule are identified. These end vessels, which are very tiny and no more than 1 mm is diameter, are cauterized using bipolar cautery eliminating the need of bulk clipping. The damage to the nerves due to dissipating thermal energy is theoretically diminished as the distance between NVBs and the prostate capsule is increased. Further mobilization of NVBs is achieved by brushing the vascular pedicles off the prostate. Hence, the prostatic fascia, NVBs, and the prostate pedicle are 'peeled of' the prostate in one piece until the urethra is reached, and NVB preservation is achieved.

In their study Zorn et al. prospectively followed 300 patients over 24 months (29). UNS was performed in 79 patients out of whom 66 were potent preoperatively (SHIM > 20), and BNS was performed on in 179 patients of which 161 where potent preoperatively. Potency was defined as the ability to achieve erections sufficient for vaginal penetration with or without the use of oral PDE5 inhibitors. In the UNS group, 52 % of the patients were potent at the end of 6 months while 62% were potent at the end of 24

months. For the group with BNS, these figures were 53% and 83% respectively.

Clipless Cautery Free Technique

Ahlering et al. have described an approach to nerve sparing using vascular clamps and sutures for pedicle control, hence claiming to protect the NVBs both from mechanical and thermal trauma (30). After the posterior dissection and releasing the prostate from its posterior attachments, the vascular pedicles are identified. These are clamped using 30 mm bulldog clamps laparoscopically and at least 1 cm from the prostate. The dissection is strictly athermal beyond this point. The pedicles are ligated using a running 3-0 polyglycolic acid suture. The clamp is then removed and the suture is used to display remaining vessels. Any pulsatile bleeding, if present along the length of NVBs is controlled by suturing. The pedicles are then divided, the lateral pelvic fascia is incised and the NVBs are gently released off the prostate, down till urethra in an antegrade fashion.

In a recent series published in 2009, Ahlering et al. selected 58 patients who were less than 65 years with an International Index of Erectile Function (IIEF)-5 score greater than 21, and followed them over 2 years prospectively (31). Potency was defined as having erections adequate for vaginal penetration with or without the use of oral PDE-5 inhibitors. The authors reported a potency rate of 40% at 3 months and 80% at 2 years for those who had UNS while for BNS, the rate was 29.3% and 93% respectively.

OTHER POTENTIAL TECHNIQUES TO IMPROVE POTENCY OUTCOMES

In addition to the techniques described above, several other techniques have been defined in other models that can be utilized in RALP. Gill et al. (32) have described a 'Clamp and Suture technique with ultrasound guidance' for laparoscopic prostatectomies. They used 25 mm atraumatic bulldog laparoscopic clamp, 4-0 polyglactin suture, and intra-operative transrectal ultrasound (TRUS) imaging before and during the application of bulldog clamps, and at the prostatectomy completion. Hence they evaluate the dimension of NVB, number of visible vessels and resistive index of the arterial flow within the NVBs. This technique completely eliminates all electrocautery, USG thermal energy, clips and bioadhesives.

Peabody et al. have described a technique where the hydrodissection of the neurovascular bundle was performed athermally by injecting 1:10000 epinephrine solution diluted with 0.9% NS into the lateral prostatic pedicle with an injection cannula needle. They performed robotic BNS in 10 patients and the series showed favorable peri-operative outcomes. However, the potency data is still awaited for these patients (33).

POTENCY OUTCOMES IN OTHER NON COMPARATIVE RALP SERIES

The definition of potency has not been consistent in the literature. The SHIM score that is used to objectively estimate the degree of erectile dysfunction is not an effective marker for potency. Most surgeons however prefer to define potency as erections sufficient to enable penetration with or without the use of oral medications (phosphodiesterase-5 inhibitors). The potency rates as reported in several studies ranges from 21.1% to 87% at 12 months post RALP (Table-1). However, these studies used different methods for patient selection and time for follow up, and some of these were reported early during the learning curve (34). Ahlering et al. have demonstrated that potency is inversely proportional to the prostate weight (35). Out of 300 consecutive men who underwent RALP by a single surgeon, they identified 139 men $\leq$ 65 years with IIEF-5 > 21. Following RALP, these were grouped according to the prostate weight and prospectively followed up over 3 months. It was found that the return to potency was inversely proportional to prostate size as 65.5% of patients who had prostate weight $\leq$ 35g were potent at 3 months vis-à-vis 14.3% who had prostate weight > 85g. They hypothesized that 1) better visualization of surgical arena due to small prostate size might allow for more preservation of nerve volume and 2) smaller prostate might reduce traction or vascular injury. In another 2 year

Table 1 *– Potency outcomes following robot assisted laparoscopic prostatectomy.*

Study	N	Evaluated Patients (N)	Inclusion Criteria	Mean Age	Follow-up (months)	Definition of Potency	% Potency UNS	% Potency BNS	% Potency Overall
Patel et al. (48)	500	200	Pre-op SHIM > 21	63.2	12	Adequate erection for vaginal penetration*	-	-	78
Bentas et al. (34)	40	37	Not clear	61.3	12	Not clear	-	-	21.1
Chien et al. (28)	80	56	At least 3 months FU and not requiring open conversion.	58.9	12	Adequate erection for vaginal penetration*	44	50	40
Costello et al. (40)	400	232	Pre-op SHIM > 21	60.2	12	Post-op SHIM > 21*	-	-	62
Joseph et al. (38)	150	55	Sexually-active patients, > 6 months post surgery	60	6-12	SHIM ≥ 22*	33.3	35.6	32.7
Lee (49)	-	-	≤ 55 yrs and pre-op SHIM ≥ 22	-	-	adequate erection for vaginal penetration*	-	-	80
Menon et al. (50)	2766	721	Pre-op SHIM > 17, > 12 months follow-up	60.2	12	adequate erection for Vaginal penetration*	-	79.2	79.2
Van der Poel & de Blok (39)	161	107	Little or no impairment of erectile function and/or IIEF > 19	59.6	6	Little or no impairment of erectile function and/or IIEF > 19	-	-	53
Tewari et al. (51)	215	215	-	60	12	-	-	87	87
Mottrie et al. (37)	184	184	-	62	12	Adequate erection for vaginal penetration*	47	70	-
Ahlering et al. (31)	200	58	≤ 65 years, IIEF-5 ≥ 22 and 24 month follow-up	57	3 24	Adequate erection for vaginal penetration*	40 80	29.3 93	32.1 89.7
Ahlering et al. (cautery, cautery free) (19)	500	36;160 38;52	41-65 years and IIEF-5 ≥ 22	56.6 56.3	3 24	Adequate erection for vaginal penetration*	0, 36.8 50, 83.3	11.5, 38.3 67.9, 94.7	8.3, 38.1 63.2, 92.0
Shikanov et al. (52)	1362	468	> 12 months of follow -up, pre-operatively potent on UCLA-PCI questionnaire	58	12	Adequate erection for vaginal penetration*		82	82

** With or without the use of oral phosphodiesterase-5 inhibitors. BNS= bilateral nerve sparing; IIEF = International Index of Erectile Function; SHIM = Sexual Health Inventory for Men; UNS = unilateral nerve sparing; UCLA-PCI = University of California Los Angeles - Prostate Cancer Index.*

prospective follow-up study, these authors reported that doubling the preserved nerve volume increased the potency by 1.36 times (UNS 50% vs. BNS 68%) for the group where cautery was used, and by 1.15 times (UNS 80% vs. BNS 93%) where cautery free technique (CFT) was used. Furthermore, the quality of erections (as estimated by IIEF-5) did not vary with the degree of NS, suggesting an important role of neural 'cross over' (19).

In another study, Mendiola et al. have reported that younger men are likely to have earlier return of potency as compared to older men (36). They classified the study population into 3 groups according to their age: < 50yrs, 50-59 yrs and ≥ 60 years. Younger men (< 50 yrs.) achieved subjective potency earlier (mean 88 days) as compared to older groups (107 and 105 days respectively, P = 0.01). Potency rates in the younger men were also significantly higher at 3 and 6 months (P = 0.04 for both), and this trend continued upto 12 months. However, no statistical significance was noted at this time, probably due to compromised power of the study.

In their retrospective series of 183 patients, Mottrie et al. have reported the post-operative sexual outcomes over a median follow-up of 6 months (37). Potency was defined as the ability to have erections adequate enough for vaginal penetration with or without the use of PDE5 inhibitors. A total of 81% of the patients younger than 60 yr and 51% of patients older than 60 years who received a nerve-sparing procedure were potent postoperatively. The potency rates were 47% and 70% for patients who had received a UNS and a BNS respectively. These results were statistically significant.

Some researchers have used a different definition of potency. In their series of 150 patients, Joseph et al. defined potency to be SHIM score > 22 (38). Only those patients who were sexually active and had a follow-up of at least 6 months post surgery were included in the study. Using this definition, the potency rates for the UNS and BNS groups were 33.3% and 35.6% respectively. In another study, Van der Poel and de Blok defined potency as little or no impairment of erectile function and/or IIEF > 19 (39). Out of 161 patients that were followed-up, 107 left the inclusion criteria. At 6 months follow-up, the potency rate was 53%. Murphy et al. defined potency as a SHIM score > 21 with or without the use of PDE5 inhibitors (40). In their series of 400 patients, 62% of patients who had a nerve sparing surgery and were previously potent regained potency after the surgery.

POTENCY OUTCOMES IN COMPARATIVE RALP SERIES

Several groups have compared the outcomes of robotic series with either open or laparoscopic series (Table-2). All these series have demonstrated that the potency outcomes are better in robotic series than in open or laparoscopic series. Tewari et al. compared 100 patients who had RRP with 200 patients who had RALP at their institution (41). Potency was defined as the ability to achieve erections adequate enough for vaginal penetration. Only patients who had a BNS and were potent pre-operatively were included in the study. The patients after RALP had a earlier return to potency as 50% regained potency at a mean follow up of 180 days after RALP as compared to 440 days after RRPs.

Krambeck et al. compared 588 RRPs with 294 RALPs (42). They defined potency as ability to have erections adequate enough for vaginal penetration with or without oral pharmacological agents. 62.8% of the patients were potent in the RRP group while 70.5 % were potent in the RALP group at the end of 12 months. In a recent comparative series, Rocco et al. compared 120 patients who had RALP with 240 patients who had open prostatectomy (43). For patients less than 65 years old who had a UNS or a BNS, the authors have reported that 73% regained potency after 12 months for the RALP group as compared to 48% for the open group. This difference was statistically significant ($p < 0.001$).

Hakimi et al. compared 75 LRPs with 75 RALPS at their institution (44). Of these 75 patients in each group, 84% and 80% of the LRP and RALP cohort were potent preoperatively, respectively. Potency was defined as the ability to have erections adequate enough for vaginal penetration more than 50% of the times. Of the patients who had a BNS, 71% of LRPs and 76.5% of RALPs were potent at 12 months post surgery. For UNS group, the figures were 40% and 57.1% respectively.

Table 2 – Potency outcomes for series comparing open, laparoscopic and robotic radical prostatectomy.

Study	Procedure Compared	N	Patients Included	Number of UNS	Number of BNS	Inclusion Criteria	Mean Age	Follow-up Months	Definition of Potency	% Potent UNS	% Potent BNS	% Potency overall
Krambeck et al. (42)	RRP RALP	588 294	-	-	-	-	61 61	12	Erections satisfactory for intercourse*	-	-	62.8 70
Ficarra et al. (53)	RRP RALP	105 103	-	-	41 64	BNS	65 61	12	IIEF > 17	-	49 81	-
Rocco et al. (43)	RRP RALP	240 120	-	-	-	All	63 63	12	Ability to have complete sexual intercourse*	-	-	41 61
Hakimi et al. (44)	LRP RALP	75 75	63 60	10 7	45 51	Preoperatively potent	59.6 59.8	12	Adequate erection for vaginal penetration > 50% of the times*	40 57.1	71.1 76.5	57.1 71.7
Jospeh et al. (54)	LRP RALP	50 50	50 50	10 1	24 46	All	61.8 59.6	3	-	-	-	22 40

** With or without the use of oral phosphodiesterase-5 inhibitors.*

CONCLUSION

RALP offers patients suffering from prostate cancer a minimally invasive approach to radical prostatectomy. In recent meta-analysis studies it has been implicated that RALP has comparable, if not better outcomes than conventional open and laparoscopic procedures. However, prospective multi-institutional randomized controlled trials need to be designed where the outcomes are evaluated by an independent third party, looking at the outcomes following different techniques. The authors advocate retrograde nerve sparing in an antegrade prostatectomy in order to minimize the risk of unintentional trauma during antegrade approach. However, regardless of the technique, wise clinical judgment should be made intra-operatively when considering nerve sparing and a careful and patient dissection should be performed athermally around the neurovascular bundles.

CONFLICT OF INTEREST

None declared.

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Correspondence address:
Dr. Vipul R. Patel
Associate Professor, Department of Urology
University of Central Florida School of Medicine
410 Celebration Place, Suite 200
Celebration, FL 34747, USA
Fax: + 1 407 303-4674
E-mail: vipul.patel.md@flhosp.org

EDITORIAL COMMENT

The paper is good and its main qualities include the fact that it was well written (in a simple and clear manner) and raised an issue that is still relevant in the field of Urology, which is the sexual outcome of radical prostatectomy.

The authors perform a review that includes the recent history of retropubic radical prostatectomy, starting with the anatomical studies of Walsh and covering the procedure's evolution, including laparoscopic and robotic prostatectomies. They appraise the surgical technique for preservation of the neurovascular bundles (NVB's) with great clarity and present comparative results between the robotic and the other forms of surgery. The strong point of this work is definitely the review of the anatomy and of the contemporary surgical techniques for preservation of the NVB's.

The authors are clear in stating that the results of the robotic surgery are comparable to those obtained through other techniques, retropubic and laparoscopic, maybe presenting a slight advantage regarding the period for return of the erectile function. Although they are deeply involved in the robotic surgery, the Authors do not present definitive results in favor of such technique, which already has 10 years of evolution.

The authors did not convey final solutions or truths about the subject, but they questioned the different criteria that are currently being used in the definition of sexual potency and appointed the need for a standardized criteria on future comparative studies.

Dr. Lisias N. Castilho
Catholic University
Campinas, SP, Brazil
E-mail: lisias@dglnet.com.br

EDITORIAL COMMENT

Robot-Assisted Laparoscopic Prostatectomy (RALP) is increasingly performed at specialized centers worldwide. The Robot is becoming an important tool for performance of minimally invasive surgical procedures around the world. With gathering experience, the technique has been shown to be feasible and reproducible.

The RALP approach offers the some advantages as laparoscopic surgery as less postoperative pain, fewer analgesics drugs and early mobilization. The magnification of the surgical field and the 3D images, allow a better view during the dissection of the neuro-vascular bundles and the urethro-vesical anastomosis. The procedure has added new hopes of reducing operative times and the learning curve for Minimally Invasive Prostatectomy.

The authors show in this paper an excellent review of Nerve-Sparing techniques and present the potency outcomes after RALP currently available in medical literature.

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

Dr. Mauricio Rubinstein
Section of Urology
Federal University of Rio de Janeiro State
Rio de Janeiro, RJ, Brazil
E-mail: mrubins74@hotmail.com

Review Article

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Novel Targeted Agents for the Treatment of Bladder Cancer: Translating Laboratory Advances into Clinical Application

Xiaoping Yang, Thomas W. Flaig

Department of Medicine, Division of Medical Oncology, University of Colorado Denver School of Medicine

ABSTRACT

Bladder cancer is a common and frequently lethal cancer. Natural history studies indicate two distinct clinical and molecular entities corresponding to invasive and non-muscle invasive disease. The high frequency of recurrence of noninvasive bladder cancer and poor survival rate of invasive bladder cancer emphasizes the need for novel therapeutic approaches. These mechanisms of tumor development and promotion in bladder cancer are strongly associated with several growth factor pathways including the fibroblast, epidermal, and the vascular endothelial growth factor pathways. In this review, efforts to translate the growing body of basic science research of novel treatments into clinical applications will be explored.

Key words: *bladder neoplasms; drug therapy; vascular endothelial growth factors; epidermal growth factors; fibroblast growth factors*

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INTRODUCTION

Bladder cancer is common with 68,810 new cases and 14,100 deaths estimated in the United States in 2008. It is the fourth most common cancer in men and the ninth most common cancer in women (1). For patients with metastatic disease, the systemic chemotherapy regimen of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) has been the foundation of systemic therapy for many years. More recently, the chemotherapy combination of gemcitabine and cisplatin (GC) has gained greater acceptance and largely replaced MVAC for the treatment of advanced bladder cancer, based on a phase III study comparing the two regimens in patients with locally advanced or metastatic bladder cancer (2). While not clearly powered as a non-inferiority trial, the 5 year overall survival was 13.0% versus 15.3% for GC and MVAC, respectively. With similar efficacy and significantly reduced toxicity, GC has been adopted as a standard, first-line regimen for advanced bladder cancer.

In the second or third-line setting, several traditional chemotherapy agents offer modest activity. Prior to the widespread use of GC, weekly gemcitabine was examined in patients with bladder cancer who had previously been treated with a platinum-based regimen with an overall response rate of 22.5% (3). These promising results lead to the development of the GC combination in the first line setting (4). Pemetrexed, a multi-targeted anti-folate agent, was more recently tested in previously treated patients with advanced bladder cancer. The objective response rate was 28% with a small number of patients experiencing a complete response; however, the median time to progression was short (less than 3 months) (5). Anti-microtubule agents are also active in bladder cancer and have been evaluated in the first and second-line setting. Paclitaxel demonstrated clear

activity in a small study of bladder cancer patients who had failed or were unfit for standard first-line therapy (6). A current first-line regimen used in patients unable to receive cisplatin-based chemotherapy combines paclitaxel, carboplatin and gemcitabine. This triple-drug combination revealed an objective response rate of 68%, with approximately half of these as complete responses (7). Additionally, a phase II trial evaluated a different taxane, docetaxel, in patients who had progressed despite cisplatin-based chemotherapy with an objective response rate of 13%, but a short duration of response, ranging from 3 to 8 months (8). The activity of docetaxel in bladder cancer was also later tested in chemotherapy-naïve patients with a higher response rate of 31% (9).

Over the last 10 years, significant advances have been made in the integration of new biologically-targeted agents in the treatment of cancer. Approximately 20% of breast cancer patients have over-expression or amplification of HER2/neu (EGFR2). Herceptin, a monoclonal antibody which targets HER2/neu, is now commonly used in breast cancer patients with HER2/neu expression yielding significant improvement in both the progression free (10) and overall survival (11). The use of single agent cetuximab (Erbitux), a monoclonal antibody against the epidermal growth factor receptor (EGFR), demonstrates significant activity in patients with advanced colorectal cancer (12). Subsequent analysis showed that patients with an activating K-ras mutation, downstream of EGFR, receive no benefit from cetuximab. This allows for the selection of an enriched K-ras wild-type treatment population, excluding those with little chance of benefit (13). Bevacizumab (Avastin) is a monoclonal antibody that binds to the vascular endothelial growth factor (VEGF), which is over-expressed in many cancer types including lung cancer. The addition of bevacizumab to standard chemotherapy significantly improves the overall survival of patients with lung cancer, although the rates of significant bleeding are increased (14). In renal cell carcinoma (RCC) traditional cytotoxic chemotherapy has little objective activity. A new class of agents, the small-molecule, multi-kinase inhibitors, have recently been approved for the treatment of advanced RCC. Both sunitinib and sorafenib target an array of pro-growth kinases including the vascular endothelial growth factor receptor (VEGFR) kinases. As documented in phase III randomized trials, sunitinib and sorafenib produce significant disease stabilization and a small number of objective responses in patients with RCC (15,16).

There are many examples of the successful use of targeted agents in modern cancer therapeutics. Despite the prevalence of bladder cancer, the availability of several potential targets in bladder cancer and the successful inhibition of these targets in many other cancer types, no biologic agents are currently in clinical use for the treatment of bladder cancer. We will review the current state of pre-clinical evaluation of targeted agents for bladder cancer and the potential impact of these agents in the clinical management of bladder cancer.

MOLECULAR PATHWAYS IN BLADDER CANCER

Two distinct developmental pathways for bladder tumors have been characterized (17). The first is that of a noninvasive papillary lesion without penetration of the epithelial basement membrane (Ta tumor). Aberrant expression of fibroblast growth factor receptor 3 (FGFR3), RAS and PIK3CA appear to play a critical role in the development of low grade and generally non-invasive bladder tumors (18). Approximately 20% of tumors are muscle invasive at diagnosis and the prognosis in these cases is poor, with less than 50% survival at 5 years (17). Tumors that penetrate the basement membrane (T1) or invade the bladder muscle (T2) are therefore much more clinically concerning and are associated with different biologic aberrancy, including common p53 mutations. These distinct pathways of tumor development with such different clinical outcomes imply that specific strategies for the management of these tumors should be developed.

FIBROBLAST GROWTH FACTOR RECEPTOR (FGFR)

Both basic science and preclinical investigations indicate that FGFR mutation and over-expression are seen commonly and occur early in the development of non-invasive bladder cancer (19).

Activating point mutations of the FGFR have been identified in approximately 40% of bladder tumors. In the FGFR family, FGFR3 is most prominent in normal urothelial cells, with only low levels of FGFR 1, 2 and 4 observed by real-time reverse transcriptase PCR (20). Further, mutations of FGFR3 are common in urothelial papillomas, which are considered to be a precursor for papillary bladder cancer, suggesting that FGFR3 mutation occurs early in the process of tumor development (21). In addition to the mutational status of FGFR3, protein overexpression of FGFR3 has been found commonly in bladder tumors, but not in normal bladder tissue (22).

Although the clinical usefulness of FGFR inhibition is not yet known, several pre-clinical evaluations have examined this approach in bladder cancer. The stable expression of a small hairpin RNA (shRNA) against FGFR3 in bladder cancer cells demonstrates an inhibition of cancer cell growth, supporting the central importance of this pathway in bladder cancer (23). Additionally, human single chain Fv antibody fragments that recognize the extracellular domain of FGFR3 have been isolated and characterized (24). This antibody inhibits ligand-binding by the wild-type receptor and has been shown to inhibit the growth of xenografts expressing FGFR3 in S249C bladder cancer cells (24). The high frequency of FGFR mutation in superficial bladder tumors suggests the possibility of utilizing an intravesical approach targeting FGFR in such patients. In vivo studies demonstrate activity using a toxic fusion protein targeting FGFR3 in human bladder cancer cells over-expressing this receptor (25).

EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR)

Compared to the FGFR pathway, targeting the epidermal growth factor receptor (EGFR) pathway is in a more mature phase, with the successful use of this approach in the clinical setting of several other cancer types. In addition, significant pre-clinical evaluation of this pathway has been undertaken. EGFR was first characterized in invasive and superficial bladder cancer in 1989 (26). Abnormal expression of the urothelial EGFR and/or altered excretion of EGF may well precede overt manifestations of transitional cell carcinoma (TCC) and thus may serve as an early marker of the invasive phenotype; the degree of EGFR overexpression in bladder tumors has been shown to correlate with tumor stage and grade (27). Laboratory investigations have shown that stimulation of the EFGR pathway both increases proliferation and the migration of bladder cancer cells (28). Work to identify the predictive markers for the response of bladder cancer cells to EGFR inhibition is underway, using a broad spectrum of bladder cancer cell lines (29). Surprisingly, there is no correlation between expression of EGF, the ligand of EGFR and the activity of EGFR inhibitors in bladder cancer cells (29). Activating mutations of EGFR, a key predictive marker for the activity of EGFR inhibitors in non-small cell lung cancer (30), are uncommon in TCC of the bladder (31).

Given the importance of EGFR in the biology of bladder cancer, a number of therapeutic strategies against EGFR to treat bladder cancer are being evaluated. Blockade of EGFR by monoclonal antibodies has been assessed in several malignancies including bladder cancer. Among several anti-EGFR monoclonal antibodies under clinical development, cetuximab (IMC-C225) inhibits EGFR downstream signaling, cell cycle arrest, angiogenesis and metastasis and is the most widely studied (32). The effect of this monoclonal antibody on bladder cancer cells in an animal model has been reported (29). Another anti-EGFR monoclonal antibody, panitumumab (ABX-EGF), has been shown to have a potent effect on several tumors such as metastatic colorectal carcinoma, although its application in bladder cancer is not known (33).

EGFR tyrosine kinase inhibitors, such as gefitinib (ZD 1839) and erlotinib (OSI-774), have been extensively studied in bladder cancer models. Preclinical data demonstrate that gefitinib selectively inhibits proliferation and angiogenesis in human bladder cancer cells (34). Erlotinib inhibits the activation of epidermal growth factor receptor, mitogen activated protein kinase, Akt and STAT3 (35,36).

HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2 (HER2/NEU)

HER2/neu overexpression and to a lesser extent, amplification, are observed in bladder cancer,

suggesting the potential utility of HER2/neu-targeted therapy in patients with advanced TCC (37). In a Japanese study of patients with bladder tumors, immunohistochemical staining demonstrated HER2/neu expression in 42.5% (38). More notably, according to the classification of grade, 60% of pT4 patients were HER2/neu positive (38). Recently, a multicenter phase II study has reported that 52.3% of metastatic urothelial carcinomas are Her2/neu positive using the DAKO HercepTest Diagnostic and fluorescence in situ hybridization (FISH) (39), consistent with the result of the Japanese group (38). The anti-tumor effect of TAK-165, a new potent inhibitor of the HER2/neu tyrosine kinase, has been studied in bladder cancer. Using a xenograft mouse model with the human bladder cancer cell (UMUC3) TAK-165 treatment resulted in 22.9% growth inhibition compared with the control group at 14 days (40).

It should be noted that the role of HER2/neu in the development of bladder cancer has not been clearly defined. Although HER2/neu is up-regulated in invasive bladder cancers, its overall expression in bladder cancer cells is less than in breast cancer cells (40). Recently, a small study reports that there is a poor association between HER2/neu protein overexpression and gene amplification, in contrast to findings in breast cancer (41). Additionally, Dinney et al. reported that the expression of HER4, but not HER2/neu or HER3, correlates with stage, grade, and survival (42). These reports raise the possibility that our understanding of the biology of HER2/neu based on breast cancer evaluations may not be directly translated into therapeutic strategies for bladder cancer.

VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF)

VEGF and its receptor are critically important in the process of angiogenesis and therefore play a vital role in the tumor growth and metastasis. The VEGF pathway was first characterized in bladder cancer in 1993 (43). While VEGF expression is observed in many patients with low or intermediate grade T1 bladder cancer, higher levels of VEGF RNA expression may be a predictor of a more aggressive form of bladder cancer with earlier cancer recurrence (44). Recent work has shown that the protein expression of VEGF in bladder cancer tissue correlates with increased tumor stage (45) and the serum levels of VEGF are directly associated with bladder cancer stage (46). VEGF binds to several cognate tyrosine kinase receptors: VEGFR1, VEGFR2 and VEGFR3. Of these, VEGFR2 appears to be the most attractive target since its expression correlates with the pathologic stage in urothelial carcinoma cell lines and bladder tumors (47).

Based on these preclinical observations, several animal studies and clinical trials have been designed for this target. Neutralizing monoclonal antibody targeted at murine VEGFR2 (DC101, ImClone Systems) has been combined with paclitaxel, with its efficacy tested in an orthotopic bladder cancer xenograft model (48). This combination demonstrated significant anti-neoplastic activity. It is likely that the observed activity is via inhibition of angiogenesis in addition to the induction of both tumor cell and endothelial cell apoptosis. The anti-tumor activity of single-agent DC101 has been examined in an orthotopic nude mouse tumor model with human 253J-BV bladder tumors (49). DC101 therapy resulted in a decrease in VEGFR-2 phosphorylation and an increase in endothelial cell and tumor cell apoptosis (49), but did not completely inhibit tumor angiogenesis when used as a single-agent (49). A VEGF-A splice variant protein conjugated with gelonin has also been utilized to target the VEGF pathway (50). Gelonin is a plant toxin with high cytotoxicity at very low doses (nM range). The VEGF-A splice variant protein serves as a targeting component to specifically guide and internalize the conjugate into the cancer cells with high VEGF expression. This fusion protein suppresses tumor growth in an orthotopic bladder cancer xenograft model (50), and has been validated in prostate and breast cancer with the goal of preventing cancer metastasis (51,52).

ANGIOGENESIS AND ITS INHIBITORS

Angiogenesis is a rate-limiting step in tumor growth and the inhibition of new blood vessel development may play a critical role in controlling tumor invasion and metastasis. The management of

bladder cancer with anti-angiogenesis strategies is still in the early phase of implementation. In addition to the VEGF pathway, other targets in the vascular compartment may be considered including the endothelin (ET)-axis and the angiopoietin-Tie pathway. The endothelin family (ET-1, ET-2, and ET-3) is a group of potent vasoconstricting peptides (53). ET-1 has been studied most extensively and has been shown to modulate endothelial cell proliferation, migration, invasion, and microtubule formation. More interestingly, ET-1 increases VEGF mRNA expression and VEGF protein levels, indicating probable cross-talk between the endothelin-axis and VEGF signaling (54). Compared with normal urothelium, increased expression of ET-1 and the associated endothelin-A- and endothelin-B-receptors has been found in the vast majority of invasive bladder cancer specimens (55). Overexpression of the endothelin-B-receptor appears to be associated with a better clinical prognosis than with the over-expression of the endothelin-A-receptor (56). Furthermore, overexpression of ET-1 is associated with up-regulation of the micro-vessel density which may impact the clinical aggressiveness of the tumor. These data suggest that the ET -axis may represent a novel therapeutic target in bladder cancer that is largely unexplored. Interestingly, the phase II clinical testing of single-agent bosentan, a dual ET-receptor antagonist, to treat stage IV melanoma patients has been reported, with stable disease noted in some patients (57). The use of atrasentan, an inhibitor of the endothelin-A-receptor, did not meet its primary endpoint of delayed time to progression in a large phase III study, but did slow the rate of prostate specific antigen rise in blood (58), additional phase III testing with atrasentan in prostate cancer is underway.

Tie2, another angiogenic pathway, has received less attention since it was only recently fully described and characterized. Tie2 is the tyrosine kinase receptor of angiopoietin-1(Ang-1) and angiopoietin-2 (Ang-2) (59,60). This pathway has an active angiogenic phase in which blood vessel differentiation by migration/sprouting is promoted; there is also a separate anti-apoptotic effect that is seen with Tie2 signaling. Interestingly, although up-regulation of Ang-1 and Ang-2 has consistently been demonstrated in many cancer types, their direct role in tumor development is controversial (61). Recently, serum levels of Ang-1, Ang-2 and Tie-2 have been examined in bladder cancer (62). High serum levels of Tie2 are correlated with shorter metastasis-free survival in both univariate and in multivariate analysis, suggesting that Tie2 expression may be an independent risk factor for metastasis.

CLINICAL USE OF TARGETED AGENTS IN UROTHELIAL CANCER

Accrual to bladder cancer trials has been poor in recent years, especially in the front-line setting (63). Accordingly, there have been a limited number of clinical trials using biologic targeted receptor kinases in bladder cancer, with many of these clinical studies only reported in abstract form. The clinical pursuit of specific agents for use in bladder cancer is based largely on the experience gained from their use for other tumor types such as lung and breast cancer.

Trastuzumab is commonly used in the treatment of breast cancer and has received significant attention as a therapeutic agent for bladder cancer in light of the HER2/neu expression seen in malignant bladder tissue. As a single agent, trastuzumab does not have clear activity against urothelial cancer. In 7 patients with transitional cell carcinoma of the bladder and HER2/neu protein over-expression, weekly trastuzumab did not yield any objective responses, although 1 patient did achieve stable disease (64). Another study examined trastuzumab in 6 patients with metastatic transitional cell carcinoma and HER2/neu overexpression by immunohistochemistry (IHC) (65). Trastuzumab was given with standard carboplatin and paclitaxel chemotherapy in 4 of the patients, with paclitaxel in 1 patient and as a single-agent in 1 patient; 2 of the participants were chemotherapy naïve. Partial responses were seen in all 6 treated patients with initial tumor regressions of 30-80%.

The largest published study to date on the use of trastuzumab in bladder cancer was led by the Southwest Oncology Group (39). Of 109 screened advanced urothelial cancer patients, 52% had HER2/neu overexpression by any method, with the majority of these as protein over-expression (49% IHC, 14% FISH, 12% serum assessment). Forty-four of

these chemotherapy-naïve patients were treated with trastuzumab, carboplatin, paclitaxel and gemcitabine. The primary endpoint of this study was the assessment of cardiac toxicity from this regimen, which was seen in 23% (grade 1-3). Secondarily, the objective response rate was 57% with five complete responses. The median time to progression was 9.3 months and the median survival was 14.1 months.

While it is difficult to make firm conclusions from these non-randomized and small studies, significant trastuzumab activity in bladder cancer has not been demonstrated to date. As we discussed earlier, while HER2/neu protein over-expression is commonly seen in bladder cancer, gene amplification is much less common (39,66), although some investigators find a better correlation with IHC status of HER2/neu and gene amplification (67). While protein over-expression of HER2/neu is a predictive marker for trastuzumab responses in breast cancer, this may not necessarily be true for bladder cancer. As with many biologic agents, the identification of predictive markers (e.g. K-ras status with cetuximab) (13) are critical to the successful testing and use of targeted agents.

Lapatinib is an orally available inhibitor of EGFR and HER2/neu, and is currently in clinical use for the treatment of breast cancer. Fifty-nine patients with locally advanced or metastatic transitional cell carcinoma with progression despite a platinum-containing front-line regimen were treated with lapatinib (68). Independent radiological review revealed 1 partial response and 18 patients with stable disease. The median time to progression was short (8.6 weeks). Additional biomarker predictors of response are being investigated.

Inhibition of the VEGFR pathway has been preliminarily examined in bladder cancer patients. A single-case report describes a man with metastatic transitional cell carcinoma and squamous differentiation treated with bevacizumab. At 24 months, the patient was reported to have minimal toxicity and a sustained response, suggesting anecdotal activity (69). Sorafenib is a multi-kinase inhibitor with prominent VEGFR inhibition. Treatment with sorafenib has been evaluated in one study of 14 patients with untreated advanced urothelial cancer (70). There were no objective responses, although 4 patients experienced stable disease; the median time to progression was 1.8 months. A second larger study examined the use of sorafenib in 27 patients with urothelial cancer with progression after front-line therapy (71). There were no objective responses noted with a median progression-free survival of 2.2 months. A related small molecule inhibitor, sunitinib, was examined as a first-line treatment in bladder cancer in those deemed unable to receive standard cisplatin-based chemotherapy. Two of 16 treated patients had a partial response and 8 participants had at least 6 months of stable disease (72). A second study of sunitinib examined patients with carcinoma of the urothelium who had progressed after 1-4 previous chemotherapy (73). In this significantly pre-treated population, 3 of 45 patients had a partial response and 11 had stable disease. While preliminary, these results suggest modest activity of sunitinib as a single-agent in bladder cancer.

In other cancer types studied, targeted therapeutic agents are generally most effective when combined with cytotoxic chemotherapy. While this is a rationale approach to explore in bladder cancer, there are very limited published data describing the combination treatments in this setting. Gefitinib, an oral EGFR inhibitor, has been evaluated with cisplatin and gemcitabine in 55 patients with advanced urothelial cancer (74). An objective response was observed in 51% with a median overall survival of 14 months. While these efficacy data are similar to standard gemcitabine and cisplatin, it is not clear that gefitinib is the most suitable biologic agent to integrate with cytotoxic chemotherapy, given the large negative studies using this approach in lung cancer (75,76).

PERSPECTIVES

The current treatment of advanced bladder cancer relies heavily on traditional cytotoxic agents, despite the tumor expression of many targets of emerging biologic agents currently available. Preclinical evaluation reveals several new agents with encouraging in vivo data, targeting FGFR, the VEGF-pathway, ET-axis, HER2/neu and EGFR. The translation of these laboratory findings into the clinical treatment of patients with urothelial cancer has

been slow, with little published information currently available. It is important to note that the accessibility of the bladder offers unique opportunities to deliver novel therapies directly to the site of the tumor, but dramatically improved accrual to bladder cancer trials will be needed to rapidly test and select the next generation of treatment for those with bladder cancer.

CONFLICT OF INTEREST

None declared.

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Correspondence address:
Dr. Thomas W. Flaig
Division of Medical Oncology
University of Colorado Denver School of Medicine
12801 E. 17th Avenue, Room L18-8117
Aurora, CO, 80045, USA
Fax: + 1 303 724-3889
E-mail: thomas.flaig@uchsc.edu

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Recovery of Hormone Sensitivity after Salvage Brachytherapy for Hormone Refractory Localized Prostate Cancer

Dan Smith, P. Nick Plowman

Department of Radiotherapy (DS, PNP), St Bartholomew's Hospital, West Smithfield, London and Department of Radiotherapy (PNP), The Cromwell Hospital, Cromwell Road, London

ABSTRACT

Purpose: Recent work has demonstrated the return of hormone sensitivity after palliative chemotherapy in androgen independent prostate cancer. We wished to establish whether a similar phenomenon existed in patients with no exposure to chemotherapy.

Materials and Methods: A review of "hormone resistant" patients who had received salvage brachytherapy for localized prostate cancer after previous external beam radiotherapy was undertaken. Three patients with subsequent biochemical relapse responded to the rechallenge with hormonal treatment.

Results: The series of patients presented here demonstrates this phenomenon occurs after salvage brachytherapy with no exposure to chemotherapy. Recovery of sensitivity is demonstrated both to androgen deprivation and to androgen receptor antagonism. The recovery of hormone sensitivity was surprisingly durable, ranging from eight months to over twenty-one months.

Conclusions: Hormone sensitivity may be recovered after salvage brachytherapy. Potential mechanisms underlying these observations are discussed and the likely central role of the activity of the androgen receptor highlighted. The relevance of these findings to the management of advanced prostate cancer is considered including thoughts on the practice of intermittent anti-androgen therapy.

Key words: *prostatic neoplasm; androgen antagonists; brachytherapy; radiotherapy*
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INTRODUCTION

Prostate cancer is unique amongst malignancies in that its initial growth is dependent on the presence of intrinsic androgens. Whilst mutations in several tumor suppressor genes have been described and are thought important in the establishment of a clonal population of cells, development of clinically significant cancer also requires an androgenic drive to cellular proliferation (1).

This necessary androgenic drive provides therapeutic targets which may be exploited to inhibit the growth of prostate cancer. Recurrent or metastatic disease is typically first treated with hormonal manipulation: strategies include testicular androgen deprivation by either bilateral orchidectomy (2) or administration of a luteinizing hormone releasing hormone (LHRH) agonist (3), and treatment with anti-androgens such as flutamide to compete with testosterone for the androgen receptor binding site (4). Intrinsic androgenic drive is thus abrogated, apoptosis of tumor cells occurs and there is subsequent tumor regression with a fall in the plasma level of prostate specific antigen (PSA).

Unfortunately, resistance to androgen suppression invariably develops: cells accumulate further genetic abnormalities and proliferate despite low testosterone levels at a median interval of 12-16 months after initiation of endocrine treatment (5).

Subsequent lines of hormonal manipulation act through related pathways and include the use of the synthetic estrogen diethylstilboestrol (6), the reduction of adrenal androgen production by administration of adrenocorticotropic hormone-suppressive glucocorticoids, e.g. hydrocortisone (7), and inhibition of the androgen synthesizing hormones 17-alpha hydroxylase and C17,20 lyase by abiraterone (8).

Conventional wisdom is that the loss of hormone sensitivity is a fixed, irreversible event, comparable to the loss of sensitivity to tamoxifen or an individual chemotherapeutic agent in breast cancer. Once the range of hormonal options is exhausted there is thought no benefit to restarting hormonal treatments to which the cancer has previously exhibited resistance.

However, the recovery of sensitivity of prostate cancer to LHRH agonist and to diethylstilboestrol has recently been reported following palliative CL56 (chlorambucil/ lomustine) chemotherapy (9) despite prior acquired resistance to both primary androgen suppression and estrogen therapy. It was postulated that the chemotherapy may have altered the subsequent behavior of the disease, particularly as a large proportion of patients with second response to estrogen therapy had been resistant to this hormone treatment immediately before chemotherapy. Similar observations have been reported after docetaxel and prednisolone therapy (10).

We describe three patients whose second response to hormone therapy occurred in a very different clinical context to those above. There was no exposure to chemotherapy as the relevant therapeutic intervention was salvage brachytherapy.

MATERIALS AND METHODS

The records of patients at our institution receiving salvage brachytherapy for recurrent localized androgen independent prostate cancer between 1999 and 2007 were reviewed. Localized relapse was diagnosed with repeat prostate biopsy after consistent PSA rise and no evidence of extraprostatic disease seen on bone scan and pelvic magnetic resonance imaging (MRI).

Patients were eligible for inclusion in this review only if they had previously been treated with conventionally fractionated external beam radiotherapy (EBRT) to 68-72Gy (a dose considered radical at the time of first treatment), had subsequently developed biochemical relapse and had initially responded to hormonal treatment before developing androgen resistance.

As salvage brachytherapy is currently unproven, patients were treated under an investigative protocol approved by the Hospital Ethics Committee and all gave full written informed consent to treatment.

Eleven men aged 54-77 were treated within this protocol. Initial results of efficacy and toxicity have been reported elsewhere (11). Nine patients have subsequently developed a further biochemical relapse and, of these, three were found to have disease which did respond to rechallenge with hormone therapy; these three are reported in detail in this manuscript.

RESULTS

Patient 1

A 56 year old man presented with Gleason 3+3 organ-confined prostate adenocarcinoma and prostate-specific antigen (PSA) of 9.9 ng/mL. He was treated with radical EBRT but achieved a PSA nadir of only 2.0 ng/mL and by 2.5 years, the PSA had risen to 7.2 ng/mL.

Goserelin was started with a PSA fall to 0.3 ng/mL, maintained for four years when the PSA rose to 1.4 ng/mL and to 3.0 ng/mL after a further two years despite ongoing goserelin. Repeat biopsy found Gleason 4+3 disease in both lobes but MRI indicated no extracapsular disease and a bone scan showed no distant disease.

Goserelin was discontinued and the patient underwent salvage ^{125}I seed brachytherapy to a marginal dose of 60 Gy. The PSA fell to 0.8 ng/mL

at three months following treatment but rose to 1.2 ng/mL and 3.6 ng/mL at nine and eighteen months respectively.

Goserelin was recommenced and the PSA became undetectable, remaining so for twelve months after restarting the LHRH agonist. At that point, goserelin was stopped and a policy of intermittent anti-androgen therapy instituted: the PSA remained undetectable for another five months before rising to the current level of 1.1 ng/mL after a further three months. Reintroduction of goserelin again led to PSA falling to an undetectable level (Figure-1).

Patient 2

A 67 year old man presented with a PSA of 11.9 ng/mL and was diagnosed with localized Gleason 5+3 adenocarcinoma of the prostate. He received radical EBRT to a dose of 70 Gy and achieved a PSA nadir of < 1 ng/mL at two years.

Repeat biopsy following a PSA rise to 4.5 ng/mL three years later yielded recurrent adenocarcinoma of the same grade, and goserelin was instituted with a PSA response to near undetectable levels. Two years later, despite continued goserelin, the PSA rose to 1.1 ng/mL, with rises to 3.3 ng/mL and 5.6 ng/mL after one and two further years respectively. The prostate was palpably hard at the right side (the site of the positive biopsy) but further staging investigations were negative for disease beyond the prostate.

Goserelin was discontinued and salvage ^{125}I seed brachytherapy was delivered to a marginal dose of 60 Gy with subsequent PSA fall over six months to 2.3 ng/mL. Nine months later PSA started rising to a peak of 21.0 ng/mL eighteen months after brachytherapy with inguinal and iliac lymphadenopathy seen on MRI.

Goserelin was reintroduced; the PSA fell to 8.5 ng/mL after six months but three months later rose to 21.8 ng/mL. Bicalutamide was added and two months later PSA fell to 6.3 ng/mL. Four months later a further PSA rise to 18.6 ng/mL occurred, bicalutamide was withdrawn with no beneficial effect and the patient declined both glucocorticoids and estrogens in favor of chemotherapy (Figure-1).

Patient 3

A 77 year old man was found to have Gleason 4+4 disease with a PSA of 40 ng/mL and extracapsular extension but no nodal or distant involvement. He received three months of neoadjuvant bicalutamide (150 mg per day) with a PSA fall to 7.4 ng/mL before radical EBRT to a dose of 70 Gy. With adjuvant bicalutamide for one year the PSA fell further to 1.6 ng/mL and the anti-androgen was discontinued.

At twelve months PSA rose to 10 ng/mL and goserelin was commenced with a PSA fall to 7.4 ng/mL six months later. Further rises to 11.2 ng/mL and 14.2 ng/mL after another six and nine months indicated progressive disease. MRI and a bone scan showed no extra-prostatic disease and with biopsy proof of Gleason 5+4 disease goserelin was stopped and brachytherapy delivered to a marginal dose of 60 Gy.

There was no significant change to the PSA at six months (14.9 ng/mL) but at one year it had risen sharply to 87.5 ng/mL with the subsequent appearance of metastatic disease. Goserelin was restarted and six months later the PSA had fallen to 23 ng/mL. A further fifteen months later the level remains stable at 25 ng/mL (Figure-1).

COMMENTS

There are limited treatment options once recurrent prostate cancer develops androgen independence. Palliative chemotherapy with docetaxel has been shown to improve survival (12) and is commonly instituted for metastatic disease following failure of maximal androgen blockade but is not suitable for all patients, particularly those with poor performance status.

Those patients with no discernible distant disease may receive local salvage treatment such as brachytherapy or cryotherapy. Salvage brachytherapy has been shown to deliver a biochemical response in patients with localized disease (13). The dose for patients who have previously received EBRT is necessarily lower than for those who have been treated without radiotherapy and is the subject of debate: whilst many clinicians treat to a marginal dose of

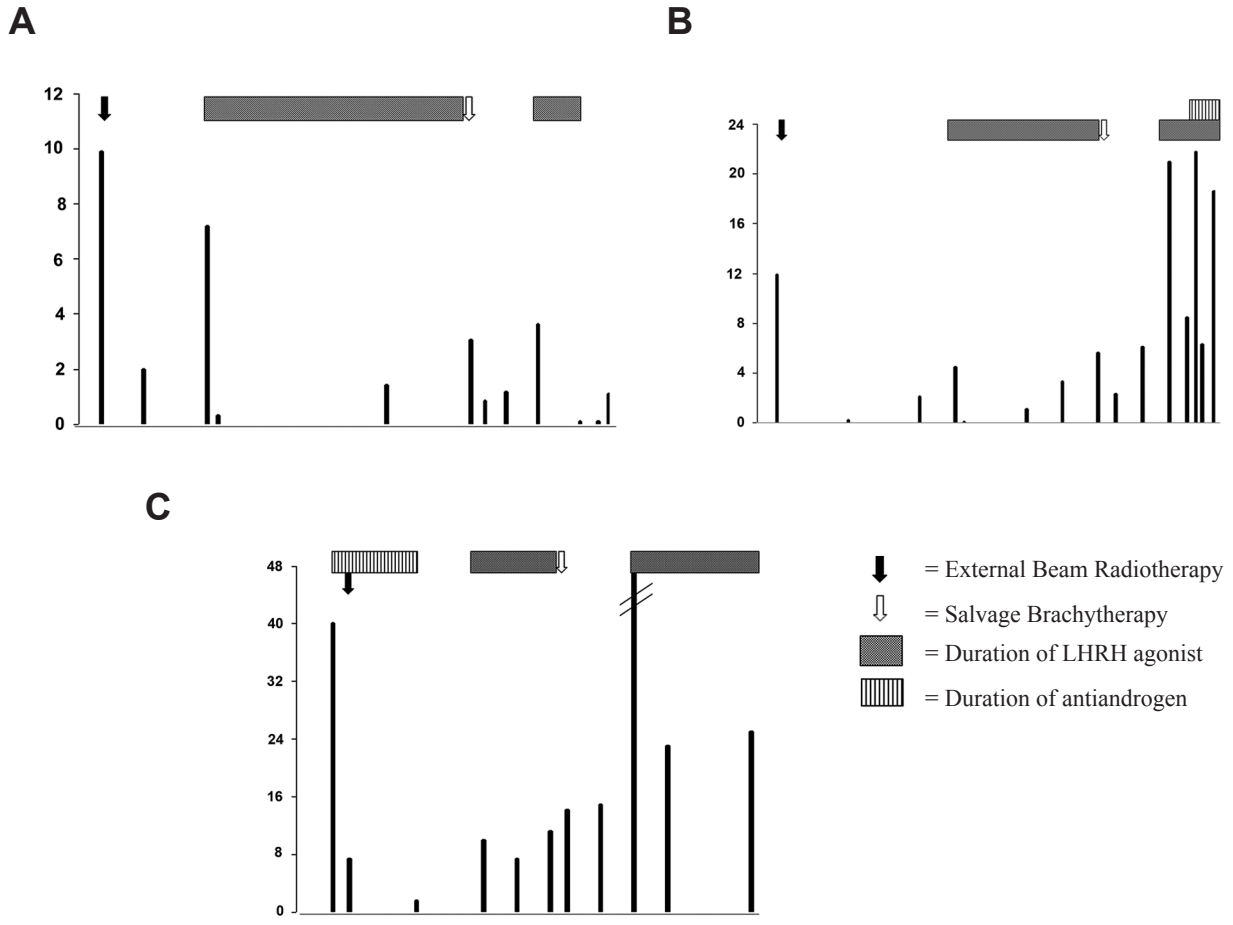

Figure 1 – *PSA level according to therapy. For time details see text. A) Patient 1, B) Patient 2, C) Patient 3.*

95-100 Gy our practice is to treat to 60 Gy using low dose rate ^{125}I seeds as this has a similar biochemical effect with a lower risk of late toxicity.

The apparent recovery of hormone sensitivity described in these three patients after brachytherapy is an unexpected finding. PSA measurement has long been accepted as a surrogate marker for disease activity as potentially more direct measures such as circulating tumor cell assays remain experimental. The phenomenon of PSA bounce (that is a transient PSA elevation following therapy) is recognized but is unlikely to be relevant to these cases: the phenomenon has not been recorded following salvage brachytherapy after previous EBRT; neither the double response to hormones in case 1 nor the response of metastatic disease in case 3 could be so explained. We believe the data support tumor progression after brachytherapy, particularly given the magnitude of PSA rise in each case. Moreover, there is the precedent for the reacquisition of hormone sensitivity in the reports following chemotherapy quoted above (9,10).

All three patients had convincing biochemical evidence of androgen independent prostate cancer but after salvage brachytherapy and subsequent biochemical failure were found to have reacquired hormone responsive disease. So good was the response in one patient (Patient 1) that the practice of intermittent endocrine therapy has been introduced. In another patient (Patient 2) the response was complete but brief and in a third (Patient 3), although the response was partial, it was remarkably durable.

Activity of the androgen receptor is key to regulation of prostate cancer and may be critical to the explanation of this observation (14). Normally, in the absence of ligand, the androgen receptor is held inactive in the cytoplasm by heat shock protein 90. Testosterone enters the prostate cell and is converted by the enzyme 5-alpha reductase to its derivative dihydrotestosterone which binds to the androgen receptor causing dimerisation. The receptor then enters the nucleus where binding at androgen responsive elements within regulatory genes, modulated by co-activators and co-repressors, causes increased transcription and cellular proliferation.

Although rarely mutated in localized disease, most androgen insensitive cell lines do show abnormalities of the gene coding for the androgen receptor including gene amplification (15), increased sensitivity to ligand (16) and inappropriate activation by other ligands (17). Thus, in a prostate cancer cell with one or more of these mutations the drive to proliferation persists despite an undetectable level of circulating testosterone.

Furthermore, mutations are known to accumulate during the life of a malignant cell and may result in a particular treatment actually becoming a stimulus for disease progression. For example it was observed that in approximately one third of patients with progression on anti-androgens, withdrawal of that treatment would lead to a PSA fall (18). Subsequently it was shown that amino acid substitutions allowed the receptor to be activated by cortisol, other steroids and even anti-androgens such as flutamide (19). Hence, withdrawal of a previously active treatment may have a beneficial effect.

The cases presented here and in previous reports indicate that the observed clinical state of androgen independence is not necessarily permanent. Whilst many of the mechanisms by which androgen dependence is lost are understood, the mechanisms by which androgen dependence is restored are uncertain.

One explanation could be that the androgen receptor itself has a degree of plasticity and that hormone sensitivity is reinduced by a mechanism perhaps triggered by a therapeutic insult. Chemotherapy has been proposed as that therapeutic insult (9) but our data suggest radiation exposure may similarly act to reverse androgen independence. Several mutations have been outlined above and it is plausible that, were further mutations to take place disabling the abnormal androgen receptor gene and hence the mechanism by which androgen resistance had developed, hormone sensitivity could be regained. This mutation may be induced by radiotherapy or potentially even arise purely from the passage of time: certainly the pelvic side wall metastases in case 2 did not receive brachytherapy.

Alternatively, androgen independent and dependent clones may coexist within a clinical cancer. The measured PSA would reflect PSA production from each clone, changes in PSA would reflect progression or response to treatment of each clone and would be most influenced by the behavior of the dominant clone. Chemotherapy and radiotherapy could act to more selectively deplete androgen independent clones, allowing residual androgen sensitive clones to become the more dominant producers of PSA, and hence the clinical cancer phenotype would seem to return to a hormone sensitive state.

A further explanation may be found in changes to downstream survival pathways, either induced by therapeutic interventions or occurring as de novo mutations. Non-androgen receptor activation pathways have been described including p53 (20) and bcl-2 (21) and disruption to these could affect tumor activity. It is important that subsequent investigations probe whether interruption to these pathways may be helpful.

Such studies may impact on the current trend towards intermittent androgen blockade in the long term care of hormone responsive metastatic prostate cancer. The rationale underlying this strategy is that continuous androgen suppression may produce a natural selection pressure in favor of androgen independent clones whereas intermittent suppression allows cytoreduction during treatment but not to the extent that insensitive clones "outcompete" sensitive clones when treatment ceases. Although clinically attractive, not least owing to presumed reduction of side effects during periods off treatment, there is not yet convincing evidence favoring the intermittent strategy and a large international trial for patients with metastatic disease is currently addressing this question following encouraging preliminary results (22).

CONCLUSIONS

The data presented here reconfirm that prostate cancer cells which have developed resistance to androgen deprivation and androgen receptor antagonism may later reacquire sensitivity to that same hormonal therapy. The data demonstrate that this phenomenon is not peculiar to patients who have received cytotoxic chemotherapy but may occur after brachytherapy, either causally related to the brachytherapy or with the passage of time.

These findings suggest that important undetermined mechanisms underlie androgen resistance and give hope that there may be therapeutic interventions available to a large cohort of patients with recurrent prostate cancer previously considered permanently androgen independent, and provoke thought as to whether the policy of intermittent androgen therapy for metastatic prostate cancer may have advantages not previously contemplated.

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CONFLICT OF INTEREST

None declared.

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Correspondence address:
Dr. P. Nick Plowman
Department of Radiotherapy
St Bartholomew's Hospital
West Smithfield, London, EC1A-7BE
Fax: + 44 20 7601-8364
E-mail: nick.plowman@bartsandthelondon.nhs.uk

EDITORIAL COMMENT

This report of cases is important to urology and oncology. The authors relate recovery of hormone sensitivity after salvage brachytherapy for hormone independent localized prostate cancer. The same phenomenon was observed before chemotherapy. The natural history of prostate cancer, i.e., hormonal sensitive replaced by insensitive cells followed by final progression can be modified. A doubt persists: can this phenomenon be applied to disseminated disease? I would like to congratulate the authors and suggests renaming this effect to "insensitive-to-sensitive hormonal retroconvertion of prostate cancer".

Dr. Daniel Seabra
Head, Urologic Oncology
Santo Amaro University
Sao Paulo, SP, Brazil
E-mail: daniel.seabra@terra.com.br

EDITORIAL COMMENT

The use of PSA as an effective marker of clinical success in the absence of measurable disease has been a boon to the evaluation of prostate cancer therapies. The selection of further treatment after a definitive therapy depends on many factors and treatment goals are prolonging survival, preventing or delaying symptoms due to disease progression, improving and maintaining quality of life, reducing treatment related morbidity.

In the past, only patients with proven metastatic disease or those with post-local therapy failures received hormonal treatment, being the androgen suppression therapy considered a mainstay of treatment only for men with advanced prostate cancer. Recent demographic changes in patients treated with hormonal therapy now include not only the patients previously mentioned, but also patients with biochemical failures, those on intermittent therapy, those at high risk for recurrence (T3-4, Gleason score ≥ 8, PSA > 20), and patients with locally advanced disease treated with radiation. Thus, the extent of disease at the time of hormonal therapy initiation and ultimate hormone refractoriness may vary considerably.

However, it is not clear whether early androgen suppression for men with locally advanced disease or asymptomatic metastases improves length and quality of life compared to androgen suppression deferred until signs and symptoms of clinical progression. The significance of prostate-specific antigen increases during the recovery of androgen after androgen deprivation therapy and radiotherapy for prostate cancer is not well understood, being a matter of intensive investigation.

An occasional patient can be salvaged with prostatectomy after a local recurrence following definitive radiation therapy; however, only about 10% of patients treated initially with external radiation therapy will have local relapse only. In these patients, prolonged disease control is often possible with hormonal therapy, with median cancer-specific survival of 6 years after local failure (1,2). Despite initial success with hormonal therapy, the durability of this response (median duration < 2 years) is inadequate, and subsequent treatment is needed for these patients. Patients with rising prostate-specific antigen (PSA) but with castrate testosterone levels still may be susceptible to hormonal therapy. If the patient is not taking an antiandrogen it should be prescribed. If the patient is already taking an antiandrogen, it should be withdrawn. Some studies have shown that withdrawal of antiandrogen may led a fall in PSA level, this is called "antiandrogen withdrawal syndrome", and its due to a mutant androgen receptor in which antiandrogen was thought to actually stimulate cell growth (3). Thus, when a rise in PSA level occurs in a patient taking an antiandrogen, the antiandrogen use should be discontinued and the patient's PSA level should be followed. Once both, antiandrogen therapy and withdrawal have been utilized, the next step is the suppression of adrenal hormones, that can account for 10% of circulating testosterone. Ketoconazole, aminoglutethimide, and hydrocortisone can suppress its production. Prostate cancer should be considered as hormonal refractory only when all of the above maneuvers have failed.

This study sought to determine whether salvage brachytherapy for localized (androgen independent prostate cancer) after previous external beam radiotherapy could lead to return of hormone sensitivity. Despite the small number of patients evaluated, doses levels inferior to what is recommended when using modern techniques of radiotherapy (Significant clinical data are available demonstrating that dose escalation radiation therapy has a significantly better outcome as the dose to the prostate is increased (4)), and patients not being accrued into any investigative protocol, the paper shows that there is a field and new possibilities for re-irradiation, with either external beam or brachytherapy.

The use of permanent (low dose rate) or temporary (high dose rate) brachytherapy after a local failure is a strategy that can to be added to the treatment arsenal, allowing both, local control and or hormone sensitivity recovery, but its indication is highly dependent on previous dose administered and toxicity reported and expected.

The salvage therapy field is an open book and patients should be advised of expected outcomes. As

an investigational procedure it should be considered ideally in a clinical trial, particularly if the patient has good prognostic factors (e.g., performance status and hemoglobin level).

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Dr. Antonio Cassio Assis Pellizzon
Head, Brachytherapy Service
AC Camargo Hospital & Prostate Institute
Oswaldo Cruz German Hospital
São Paulo, SP, Brazil
E-mail: cassiopellizzon@aol.com

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Undergrading and Understaging in Patients with Clinically Insignificant Prostate Cancer who Underwent Radical Prostatectomy

Irai S. Oliveira, Jose Pontes-Junior, Daniel K. Abe, Alexandre Crippa, Marcos F. Dall'Oglio, Adriano J. Nesralah, Katia R. M. Leite, Sabrina T. Reis, Miguel Srougi

Urology Department, University of Sao Paulo Medical School, Sao Paulo, Brazil

ABSTRACT

Purpose: The aim of our study is to evaluate the undergrading and understaging rates in patients with clinically localized insignificant prostate cancer who underwent radical prostatectomy.
Materials and Methods: Between July 2005 and July 2008, 406 patients underwent radical prostatectomy for clinical localized prostate cancer in our hospital. Based on preoperative data, 93 of these patients fulfilled our criteria of non-significance: Gleason score < 7, stage T1c, PSA < 10 ng/mL and percentage of affected fragments less than 25%. The pathologic stage and Gleason score were compared to preoperative data to evaluate the rate of understaging and undergrading. The biochemical recurrence free survival of these operated insignificant cancers were also evaluated.
Results: On surgical specimen analysis 74.7% of patients had Gleason score of 6 or less and 25.3% had Gleason 7 or greater. Furthermore 8.3% of cases showed extracapsular extension. After 36 months of follow-up 3.4% had biochemical recurrence, defined by a PSA above 0.4 ng/mL.
Conclusions: Despite the limited number of cases, we have found considerable rates of undergrading and understaging in patients with prostate cancer whose current definitions classified them as candidates for active surveillance. According to our results the current definition seems inadequate as up to a third of patients had higher grade or cancer outside the prostate.

Key words: *prostate neoplasms; Gleason score; prostatectomy*
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INTRODUCTION

Prostate cancer (PC) is the most commonly diagnosed malignancy among males in western countries. Autopsy studies estimate that 30% of men over 50 years harbors histological PC (1,2), but the chance of clinical diagnosis is much lower, being approximately 11% during lifetime (3), meaning that not all PC needs curative treatment. According to Epstein et al. (4), 16% of nonpalpable PC diagnosed by screening techniques is insignificant and may be safely managed conservatively.

For this reason, active surveillance protocols have been proposed as an option for patients with both low grade and stage, and several studies to date have shown the feasibility of treating localized PC by expectant or conservative procedures with good results (5). These studies reported a dropout rate of 25 to 30% driven mainly by tumor progression or patient and physician anxiety.

The main factor determining success in active surveillance protocols is the proper selection of patients. Due to the large PC heterogeneity, it is of paramount importance to distinguish the patients with

biologically aggressive tumors that need definitive treatment from those with an indolent tumor that benefits more by active surveillance (5,6).

Currently, the patients are selected accordingly to specific findings at biopsy and clinical stage, but the criteria of clinical non-significance are variable. The most widely accepted is the Epstein criteria, which consist of prostatic specific antigen (PSA) density 0.1-0.15, low or intermediate cancer grade, core involvement less than 3 mm and involvement of only one needle biopsy core (4). These criteria are used to predict the presence of clinically insignificant tumor, defined by Gleason patterns less than 4, tumor volume less than 0.5 cm^3 and organ-confined disease (4).

However, one should not forget the known existence of understaging and undergrading for any neoplasm which can erroneously engage patients in expectant management when local treatment was the best option.

The incorrect staging and grading is a real threat to any active surveillance protocol. A study evaluating surgical specimens of patients with PSA less than 10 ng/mL, which is associated with lower stages, showed extra-capsular extension or seminal vesicle involvement in 10% and 3% of cases respectively (7).

Furthermore, Gleason score discordance between biopsy and surgical specimen has been estimated to vary between 47 to 69% (8,9). A meta-analysis involving over 14,000 patients, found that the Gleason graduation of prostatectomy was correctly anticipated by the biopsy in 63% of the patients. Interestingly, among all patients with high-grade tumor in the surgical specimen, 67% had tumors of low or moderate grade in the biopsy, indicating a higher risk of undergrading for these patients (10).

In conclusion, these studies reflects the inaccuracy of current staging and grading regarding the true insignificance of PC, meaning that selection of patients is of crucial importance in active surveillance protocols. The aim of this study was to compare data of prostate biopsy with the results of surgical specimen of patients with clinically insignificant operated PC, in order to evaluate the rate of undergrading and understaging. We also evaluated the biochemical recurrence free survival for these patients.

MATERIALS AND METHODS

Between July 2005 and July 2008 a group of 406 men diagnosed with localized PC underwent radical prostatectomy at our institution. From this group, we selected the patients whose tumor was diagnosed by an extended biopsy protocol and who fulfilled the following criteria of non-significance: preoperative PSA less than or equal to 10 ng/mL, staging clinical T1c, transrectal prostate biopsy with Gleason grading less than or equal to 6, no pattern Gleason 4 or 5 and percentage of affected fragments less than or equal to 25% (Table-1). Patients who received hormone therapy before surgery were excluded. Considering these criteria, 93 patients were selected for this analysis.

The following surgical pathology data was recorded: Gleason score, pathological staging, seminal vesicle invasion, microvascular and perineural invasion, extracapsular invasion, bladder neck invasion, positive margin and total weight of prostate. Unfortunately, tumoral volume, an important predictor of biological behavior, is not a parameter routinely measured in our institution and was not recorded.

We compared the Gleason score concordance between biopsy and surgical specimen and the percentage of patients with locally advanced disease, attempting to estimate the number of patients erroneously classified as candidates to active surveillance. The biochemical recurrence free survival was calculated considering recurrence as a PSA above 0.4 ng/mL.

Statistical Analyses

The chi-square test was employed to evaluate the difference of the Gleason score between biopsy

Table 1 *– Definition of clinically insignificant prostate cancer.*

PSA preoperative	< 10 ng/mL
Clinical stage	T1c
Gleason score in biopsy	≤ 6
% of positive cores in biopsy	≤ 25%

PSA = protein-specific antigen.

Table 2 *– Demographic data.*

Variable	N. of Patients
Total	93
Age (mean)	65.7 years (range 48 - 79)
PSA preoperative (mean)	6.03 ng/mL (2.5 - 9.7)
N. of cores in biopsy (mean)	12.01 (10 - 18)
% of positive cores (mean)	14.6 % (5.6 - 25%)

PSA = prostatic specific antigen.

Table 3 *– The comparison of Gleason scores between biopsy and surgical specimen in 87 cases.*

	Surgical Specimen					
Biopsy	4	5	6	7	8	Total
4	0	0	1	1	0	2
5	0	0	2	2	0	4
6	0	2	60	16	3	81
Total	0	2	63	19	3	87

Chi-square $p < 0.001$

and surgical specimen and a p value < 0.05 was considered statically significant. For other variables the statistical methods consisted of descriptive and categorical analyses.

RESULTS

The average age of patients was 65.7 years and the mean PSA was 6.03 ng/mL. The average percentage of positive fragments on biopsy was 14.6%. The complete demographic data is depicted in Table-2.

The comparison of Gleason score between biopsy and surgical specimen was possible in 87 cases and the results are displayed in Table-3. According to this table, 77.9% of cases showed the same Gleason score, while upgrading and undergrading occurred in 19.5% and 2.6% of cases, respectively. Employing the Chi-square test, a significant difference ($p < 0.001$) of Gleason score between radical prostatectomy specimen and biopsy was observed, being important to note that 25% of clinically insignificant PC showed Gleason score higher than 6 at surgery.

Regarding the pathological stage, data was available for 84 patients of which 90.4% had organ confined disease (Table-4). Additional surgical pathology data is showed in Table-5.

After 36 months of follow-up only three patients (3.4%) had biochemical recurrence defined as a PSA greater than or equal to 0.4 ng/mL.

COMMENTS

The discrepancy between the Gleason score observed at the biopsy and surgical specimen may

Table 4 *– Pathological stage (TNM) of patients.*

Pathological Stage	N. of Patients
T0	3 (3.6%)
T2	73 (86.9%)
T3	8 (9.5%)
Total	84 (100%)

TNM = tumor, node, metastasis.

Table 5 *– Pathological characteristics of surgical specimens of radical prostatectomy.*

	Present	Absent
Invasion of seminal vesicles	6 (7.1%)	78 (92.9%)
Extracapsular extension	7 (8.3%)	77 (92.0%)
Invasion of bladder neck	1 (1.2%)	83 (98.8%)
Positive margin	6 (7.1%)	78 (92.9%)

result in improper assessment of the disease and treatment, which can influence the prognosis of an individual patient, specially if active surveillance is proposed. Therefore, the correct stage and grade is of paramount importance in the treatment decision for any neoplasm.

In our series, we found a substantial Gleason score disagreement between biopsy and surgical specimen in patients that fulfilled active surveillance requirements ($p < 0.001$). Within a group of patients with non palpable tumors of low grade, 25% had Gleason score of 7 or greater in the surgical specimen, reflecting the inadequacy of grade prediction with the current employed methods.

The undergrading rate of 25% underscores the risk and consequence of incorrect grade evaluation at biopsy in a group of patients that would be assigned to conservative management. In accordance to our results, Müntener et al. evaluating 6625 patients found an identical Gleason score in biopsy and surgical specimens only in a third of patients (8). In a contemporary series of 1,455 men who underwent radical prostatectomy at John Hopkins, although the rate of undergrading was smaller than before, the disagreement between biopsy and radical prostatectomy Gleason score was seen in 24% of cases (11), a rate similar to that observed in our study.

An important aspect of our results is that PC diagnosis was made through extended biopsy protocols, which is known to improve diagnosis and reduce the sampling error that is intrinsic to the ultrasound-guided prostate biopsy. The better performance of extended biopsy when compared to fewer samplings schemes can be exemplified by the Nesrallah's study, who found PC detection rates of 75% and 88% when 6 or 14 cores were respectively sampled (12). However, our undergrading rate was considered significant even when employing extended biopsy.

The precise staging is also important for adequate PC management. In our series of clinically insignificant patients, despite 3 cases that showed pT0, we found non organ confined disease in 9.5% of cases. This finding is a known negative prognostic factor in PC and does not qualify these tumors as being indolent.

A lower PSA is associated with organ confined tumor and is a common requisite of any clinically insignificant criteria, however there is sufficient data indicating that lower PSA is not always associated with indolent PC. A study evaluating surgical specimens of patients with PSA less than 4.0 ng/mL revealed extra-prostatic extension or positive margin in 8.3% of cases (13). Likewise, Geary et al. (7) found positive surgical margins in 13% of non palpable tumors with PSA between 4 and 10 ng/mL.

It is noteworthy, that in our series the error related to staging (9.5%) was lower than the error rate related to grade assignment (25%), a finding that was also observed by others (14), which indicates that new methods should be particularly developed to improve grade prediction in PC.

Considering the undergrading and understaging together, we observed that up to a third of our patients with clinically insignificant tumors displayed unfavorable findings at radical prostatectomy. In agreement with our results, Chun et al. evaluating patients with clinically insignificant tumor found that 33% had pathological Gleason score of 7 to 10 or non organ confined tumor at surgical specimen (15). Even when the cohort was restricted to patients who also had PSA < 10 and T1c clinical stage the rate of unfavorable cancer was 28% (15).

Similarly, D'Amico et al. evaluated 66 men with PC diagnosed on the basis of a single microscopic examination of adenocarcinoma, and found extracapsular extension in 4% and positive margin in 6% of cases (16). It is important to mention that 10% of these patients failed biochemically within 5 years after radical prostatectomy.

Even after a short follow-up period, we observed that three patients (3.4%) had biochemical recurrence. Likewise, a systematic review of operated small-volume cancer on biopsy showed biochemical recurrence in 8.6% of cases (range 6.1%-12.1%) (17). These data emphasize the fact that even clinically insignificant cancer may not be cured by radical prostatectomy.

We believe that active surveillance is an adequate treatment for PC, however a considerable proportion of patient candidates for this modality of treatment have "significant" features at surgical specimen. Our data indicates that current criteria to select patients for active surveillance seems inappropriate, as once up to a third of these patients clearly do not have insignificant tumors; in fact, they would be exposed to mortality by PC if the tumor was left untreated.

In accordance to our conclusion, a recent validation of Epstein criteria in European men showed that 24% of the patients who fulfilled the criteria had unfavorable characteristics at radical prostatectomy (14). The authors conclude that the widely used Epstein criteria underestimate the true nature of PC and that caution is advised when treatment decisions are based solely on this single criterion (14).

Corroborating this observation, Goto et al. evaluated 170 surgical specimens whose data fulfill the Ohori criteria of non-significance, which are PSA density less than 0.1, clinical stage T1c and maximum length of cancer of 2 mm in any core, and found that 25% of specimens showed significant PC (18). These two series, along with ours, indicate that the undergrading and understaging rates are similar in clinically insignificant PC whatever the criteria employed.

It is important to note that the Epstein criteria were largely validated (14,19) and, although not perfectly accurate, remain the better alternative for prediction of clinically insignificant PC when compared to other definitions (18,20). The Epstein criteria are more accurate, for example, than the Kattan nomogram whose accuracy is between 64% and 79% (20).

The addition of molecular biology data may add to the predictive accuracy of the existing criteria for clinical non-significance, as demonstrate by Kattan et al. that increased the accuracy of biochemical recurrence prediction by adding TGF-β e interleukin 6 levels in previous nomogram (21). The inclusion of PSA derivatives may also improve prediction and a study evaluating 163 radical prostatectomy specimens of stage T1c showed that the addition of free PSA increased the accuracy of Epstein criteria (22).

We recognize that our small patient population is a limitation to our conclusions, due to the fact that our institution is a tertiary health care center that receives the more complex and advanced cases. Therefore, only a few of our operated patients could be included in this analysis. Nevertheless, based in our results, other criteria should be developed in order to improve the non-significance factor and selection of PC patients, and to reduce the understaging and undergrading rates.

CONCLUSION

Although the expectant management for PC is a valid alternative treatment of properly selected cases, after analyzing our data we conclude that special care should be taken when including patients in this modality of treatment, because the risk of under staging and under grading seems substantial even in these properly selected cases.

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CONFLICT OF INTEREST

None declared.

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Correspondence address:
José Pontes Jr.
Av. Dr. Arnaldo, 455 / 2nd floor LIM 55
Sao Paulo, SP, 01246-903, Brazil
Fax: + 55 11 3061-7183
E-mail: docjpjr@uol.com.br

EDITORIAL COMMENT

In this study, Santana de Oliveira et al. (1) report on how current criteria for clinically insignificant prostate cancer (PCa) work in their series which includes less than 100 cases. This is an important limitation to the study design; likewise, the paper is of interest since insignificant PCa is an important topic in daily practice. As shown by Santana de Oliveira et al. (1) we do not have a reliable model to predict insignificant prostate cancer in every single patient. Prediction of clinically insignificant prostate cancer (PCa) remains as a major problem in clinical practice. In the updated format, the contemporary Epstein criteria represent the most widely used tool for prediction of clinically insignificant prostate cancer, in spite of limitations. Of 217 patients with organ confined disease, 18 (7.6%) had Gleason sum 7 or higher in the series used to update the Epstein criteria. Therefore, 199 of 237 patients (83.9%) in the updated Epstein criteria series had both organ-confined disease and favorable (Gleason 6 or lower) prostate cancer grade. This finding indicates that the updated Epstein criteria underestimated disease stage and/or grade in 16% of North American patients and were accurate in 84% of predictions. Conversely, the rate of Gleason sum 7 was substantially higher in Brazilian population (25.3%) which yielded substantially lower overall accuracy (74.7%) than the one reported in North America (84%); the Brazilian cohort refers to 12 (10-18) cores per case just similar to the Hopkins study that refers to 12 core biopsies. Therefore, it may be argued that the stage and grade migration that results in the detection of an increasing proportion of Gleason 6 prostate cancer may result in lower error rate of the Epstein clinically insignificant prostate cancer criteria, when these are compared with Brazilian findings (1-2). The authors (1) provide an in depth review of the various causes leading to failure of the contemporary Epstein's criteria. An important issue derived from the current study deserves a comment since it is related to the diagnostic rate of Gleason 7; this grade is heterogeneous and represents the most complex exercise in needle prostate biopsies sign out, and differences in the performance of the Epstein criteria between North America and Brazil may explain by itself the observed differences seen in the current study. The results by Santana de Oliveira et al. (1)

emphasize the need for continuing education activities concerning Gleason grading in order to achieve the maximum accuracy and reproducibility in daily practice of prostate pathology.

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Dr. Antonio Lopez Beltran
Department of Pathology, School of Medicine
University of Cordoba
Cordoba, Spain
E-mail: em1lobea@uco.es

Dr. Rodolfo Montironi
Institute of Pathological Anatomy
Polytechnic University of the Marche Region
Ancona, Italy

Dr. Liang Cheng
Department of Pathology and Laboratory Medicine
Indiana University School of Medicine
Indianapolis, IN, USA

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Complete Androgen Blockade Safely Allows for Delay of Cytotoxic Chemotherapy in Castration Refractory Prostate Cancer

Rafael A. Kaliks, Patricia Santi, Ana P. Cardoso, Auro Del Giglio

Oncology Department (RAK), Hospital Israelita Albert Einstein, Sao Paulo and Division of Oncology and Hematology (PS, APC, ADG), ABC Foundation School of Medicine, Santo Andre, Brazil

ABSTRACT

Purpose: Complete androgen blockade (CAB) does not prolong overall survival (OS) in patients with castration refractory prostate cancer (CRPC). Although there is variable clinical benefit with second-line hormone manipulation, we do not know which patients might benefit the most.
Objectives: To identify clinical predictors of benefit of complete androgen blockade.
Materials and Methods: We reviewed the records for 54 patients who received treatment with CAB in the setting of disease progression despite castration. We evaluated progression-free survival (PFS) and OS according to PSA at diagnosis, Gleason scores, age, testosterone level, and duration of prior disease control during castration in first line treatment.
Results: Among 54 patients who received CAB, the median PFS was 9 months (CI 4.3-13.7) and OS was 36 months (CI 24-48). We did not find an effect of PSA at diagnosis ($p = 0.32$), Gleason score ($p = 0.91$), age ($p = 0.69$) or disease control during castration ($p = 0.87$) on PFS or OS. Thirty-four patients subsequently received chemotherapy, with a mean OS of 21 months (CI 16.4-25.5, median not reached).
Conclusion: Age, Gleason score, PSA at diagnosis and length of disease control with castration did not affect PFS or OS. In the absence of predictors of benefit, CAB should still be considered in CRPC.

Key words: *prostatic neoplasms; castration; drug therapy; neoplasm metastasis; docetaxel*
Int Braz J Urol. 2010; 36: 300-7

INTRODUCTION

The introduction of screening for prostate cancer through the use of prostate specific antigen (PSA) measurements has predictably increased the detection of prostate cancer, while an expected shift toward earlier diagnosis was also observed (1). Despite the trend to earlier diagnosis, there are still a significant number of patients who are diagnosed with metastatic disease. Metastatic prostate cancer is treated with androgen deprivation.

According to the American Society of Clinical Oncology and the European Association of Urology guidelines, the current first-line treatment of metastatic prostate cancer consists of either surgical castration (orchiectomy) or chemical castration with the use of luteinizing hormone releasing hormone analog (LHRHa). Both societies contemplate the association of an androgen receptor blocker (ARB) with castration upfront, a combination known as complete androgen blockade (CAB), as a valid alternative to castration. Although the length of metastatic disease control with castration alone is largely variable, the disease eventually progresses after an average 24 months (2,3). CAB as first-line treatment has been the subject of several clinical trials and meta-analysis (3-5). CAB has shown

to be better in terms of progression-free survival and in terms of overall survival compared to castration if non-steroidal rather than steroidal ARBs are used (3-6), but at the cost of greater toxicity. Although CAB should therefore be considered as a good treatment alternative upfront, the most widely used first line hormone manipulation consists of castration alone. For patients who have had progressive disease despite castration, the addition of an ARB has shown modest impact in terms of PSA response, limited benefit in terms of disease progression and no benefit in terms of overall survival (6,7), though at low cost and only modest toxicity. The vast heterogeneity of patients' disease at the time they fail castration as well as the variable nomenclature used to define the status of hormone responsiveness (i.e. castration-refractory vs. hormone-independent) have hampered efforts to clearly define which patients with metastatic prostate cancer might benefit and should therefore be offered CAB after castration. It is important to recognize that castration-refractory prostate cancer (CRPC) is a different entity than hormone-independent prostate cancer, for which the definition includes not only a castrate level of testosterone, but also the progression of disease after at least two lines of hormone manipulation or anti-androgen withdrawal. With the publication of two large phase III studies showing prolongation of survival (by about two months) with docetaxel-based chemotherapy (8,9) it became more common to treat patients with docetaxel-based therapy immediately after the development of CRPC. Thus, progressively fewer patients receive a trial of CAB.

The main difficulty in deciding which patients should be offered second-line and even third-line hormone manipulation resides in the variability of clinical benefit when CAB is given after castration, and in the fact that CAB has never been shown to prolong survival when given to these patients (10,11) as opposed to first-line (5). Recent data show that the role of the androgen receptor in signaling pathways is maintained and leads to disease progression even after the failure of chemotherapy (12). This has renewed the interest in identifying which patients may benefit from sequential hormone manipulation.

Here, we investigated the effect of several clinical variables on progression-free survival (PFS) and overall survival (OS) in patients with CRPC treated with CAB. The variables studied were PSA at diagnosis, Gleason score, age, length of duration of disease control on prior castration, and testosterone level prior to initiation of CAB.

MATERIALS AND METHODS

We reviewed the medical records for all the patients with prostate cancer who received treatment at the ABC Foundation School of Medicine, Brazil, between September 2005 and December 2008. Patients selected had documented bone and/or soft tissue metastasis and had received at least one month of CAB, consisting of the combination of flutamide 250 mg tid and castration. All patients had been treated with either chemical or surgical castration prior to initiation of CAB, and the disease had progressed despite castration. Prior to initiation of CAB, all patients were evaluated with testosterone levels (had to be < 50 ng/dl), alkaline phosphatase, PSA, lactic dehydrogenase, bone and computer tomography (CT) scans. Disease progression was defined as previously published (13): evidence of progressive soft tissue or lymph-node metastasis, evidence of new bone lesions or an increase in at least 25% of PSA above the nadir level. PSA, alkaline phosphatase, and lactic dehydrogenase were measured at two-month intervals or shorter. In the event of abnormal lab results or worsening pain suggesting disease progression, new bone and CT scans were done. As long as alkaline phosphatase and lactic dehydrogenase were stable and within normal limits, and as long as PSA and symptoms were stable, both bone and CT-scans were limited to every six months. Upon disease progression during treatment with CAB, all patients received zoledronate 4 mg IV monthly. We followed patients on treatment to evaluate disease progression, and obtained information regarding tolerability and efficacy of subsequent treatment with either third line hormone therapy or chemotherapy. Chemotherapy consisted of a standard docetaxel-based regimen.

We assessed OS and PFS during CAB using Kaplan-Meyer plots. We analyzed the effect of age, Gleason score, PSA at diagnosis, and duration of disease control with castration on OS and PFS using

Table 1 – *Patients' characteristics.*

	N = 54	%
Surgical castration	37	69
Chemical castration (aLHRH)	17	31
Bone metastasis	54	100
Soft Tissue Metastasis	5	9
	Median	Range
Age (years)	69	50-90
Gleason score	7	4 to 10
PSA at diagnosis (ng/ml)	53	2-1815
PFS on prior castration (months)	12.5	1-103

aLHRH = Luteinizing hormone releasing hormone analog; ARB = androgen receptor blocker; PSA = prostate specific antigen; PFS = progression-free survival.

Cox proportional hazards. Testosterone levels at the initiation of CAB and its correlation with PFS was also evaluated by dispersion diagram. Toxicity was assessed based on medical records data. For patients who developed progressive disease, one month of ARB withdrawal was mandatory before initiation of chemotherapy. All statistical analyses were performed using SPSS 15.0 software.

RESULTS

The study was conducted between September 2005 and December 2008. We identified 54 castrated patients with metastatic prostate cancer who received CAB after failing castration. Patients included in this study received at least one month of flutamide in addition to preexisting castration. All patients had documented bone metastasis. Patients' characteristics are shown in Table-1.

With a median follow up of 21 months (range 1 to 66 months), median PFS was 9 months (CI 4.3-13.7), as shown in Figure-1. PFS did not correlate with age (p = 0.69), Gleason score (p = 0.91), PSA at diagnosis (p = 0.32) or length of castration (p = 0.87) using Cox regression analysis, as shown in Table-2. Multivariate analysis also failed to show an effect of these variables on PFS. Regarding testosterone levels, the dispersion diagram showed no correlation with PFS (data not shown).

Median OS from initiation of CAB was 36 months (CI 24-48), as shown in Figure-2. As with PFS, OS was not affected by age, PSA, Gleason score or duration of disease control during castration on Cox regression analysis (Figure-2). Overall survival for all patients since initiation of castration was 80 months

Table 2 – *Effect of clinical variables on progression-free survival and overall survival.*

	Overall Survival			Progression-free Survival		
Variable	HR	95% CI	p Value*	HR	95% CI	p Value*
Age (years)	0.96	[0.91; 1.02]	0.171	0.99	[0.96; 1.03]	0.693
Gleason score	0.93	[0.61; 1.42]	0.727	0.99	[0.75;1.30]	0.917
PSA at diagnosis (x 50ng/ml)	1.06	[0.99;1.14]	0.088	1.03	[0.97;1.10]	0.329
PFS on castration (months)	0.99	[0.96;1.01]	0.302	1.00	[0.99;1.02]	0.870

** Results by univariate Cox Regression; HR = hazard ratio; PSA = prostate specific antigen; PFS = progression-free survival.*

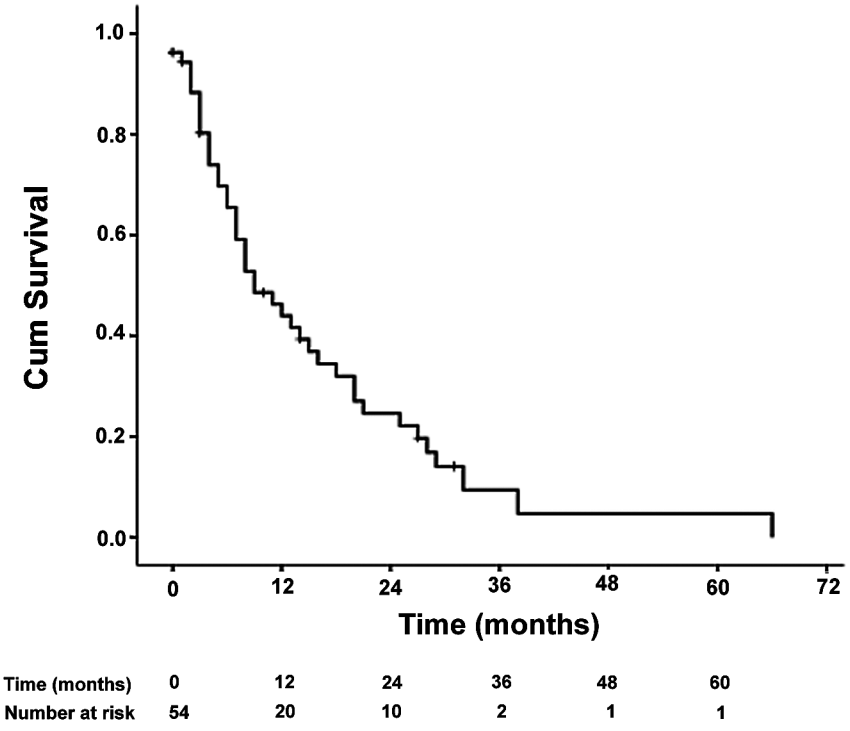

Figure 1 *– Progression free survival from complete androgen blockade.*

(CI 49-110), with the caveat that several patients had initiated castration based on PSA relapse alone, and subsequently developed metastasis.

After disease progression on CAB, 12 patients received third-line hormone manipulation consisting of high dose ketoconazole or diethylstilbestrol, with a PFS of 6 months (CI 2.9-9.1). A total of 34 patients received chemotherapy after having progressive disease despite CAB. Chemotherapy consisted of docetaxel-based regimen in all but two patients, who received mitoxantrone. Median OS was not reached due to short follow-up, while mean survival was 21 months (CI 16.4-25.5).

Overall, toxicity attributed to CAB was low. We identified only one patient who experienced limiting toxicity to the liver and had to interrupt CAB. Although there were cases of nausea, gynecomastia, worsening fatigue, mild elevation in liver function tests and malaise, these events were rare. The only patient who experienced significant elevation in transaminases and bilirubin fully recovered, but required chemotherapy shortly thereafter due to disease progression. No information on pain control was available that allowed further conclusions.

COMMENTS

In this study, we showed that after failure of castration, the use of CAB lead to a median PFS of 9 months, which is significantly longer than previously reported (7,10,11). It is well known though that the widely variable disease behavior in this patient population makes it difficult to compare our cohort of patients with other series. In our study, prior to initiating CAB, some patients were already castrated in the setting of metastatic disease, while others were

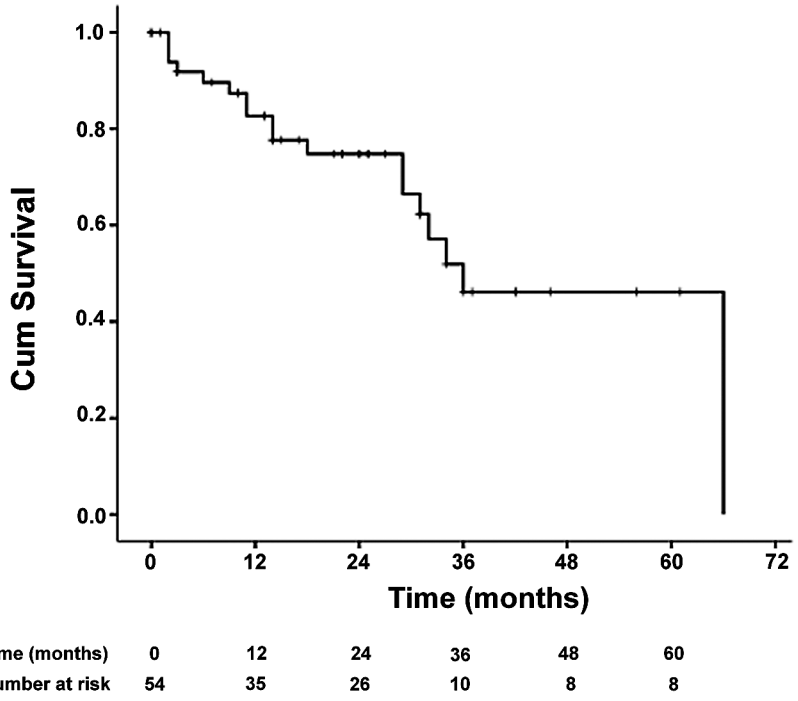

Figure 2 – *Overall survival from initiation of complete androgen blockade.*

castrated after PSA-relapse only. This variability alone may have affected our rather long PFS.

In localized prostate cancer, CAB has led to long-term remissions, even raising discussion about possible cure (13,14). In metastatic disease, although more toxic than castration alone, data show that CAB prolongs survival when used as first-line manipulation (5). CAB does not seem to prolong overall survival when used during subsequent treatment (7,10,11). Before docetaxel became the standard treatment for CRPC, most patients received sequential hormone manipulations with variable success in controlling the disease. No predictive markers have yet been found that identify the patients who benefit from these sequential hormonal treatments. Our analysis found no correlation between the clinical variables here studied and PFS or OS. Although the number of patients is a clear limitation of the study, our results suggest that Gleason score, length of duration of castration, PSA and age do not fulfill the need for predictive markers. Preliminary data in the literature suggest that PSA-doubling time (PSAdt) may correlate with the benefit of subsequent treatment in hormone-refractory disease (15). Unfortunately, due to the retrospective nature of our study and the variable pattern of patient follow-up during initial castration, data on PSAdt are not available.

As the addition of an ARB would block the effect of residual adrenal-derived testosterone, we would expect that the higher the residual testosterone (even within castration levels), the greater the benefit of CAB. We could not confirm this hypothesis, which seems to support the current concept that the persistent sensitivity to hormone manipulation may not be limited to the effect of circulating androgens. Rather, it supports the notion of a persistent role for the androgen-receptor signaling in the oncogenic mechanism, even in the so-called androgen-independent state (12,16).

Although docetaxel-based therapy has become a standard treatment for CRPC, there is clearly still room for hormone manipulation after castration (possibly even for third-line manipulation in selected cases). The strategy to reliably identify the patients who may benefit from CAB is still to be described. Recent data show significant response to abiraterone (12,16), as well as to a second-generation anti-androgen (17), suggesting that hormone manipulation may be further optimized. In fact, these novel agents may replace docetaxel as the first line treatment for CRPC in the near future.

Novel strategies to prolong disease control with hormone manipulation are being investigated, such as the concomitant use of epigenetically-targeted therapies (18,19) and endothelin-A receptor antagonists (20). Adequate patient selection for such alternative treatments still remains a challenge.

CONCLUSIONS

CAB can lead to disease control in patients with CRPC. Age, Gleason score, PSA at diagnosis and length of disease control with castration did not affect progression-free or overall survival. In the absence of predictors of benefit, CAB can still be considered in castration-refractory prostate cancer.

CONFLICT OF INTEREST

None declared.

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Correspondence address:
Dr. Rafael A. Kaliks
Hospital Israelita Albert Einstein
Av. Albert Einstein 627/701, 2º andar, BL-A
Sao Paulo, SP, 05652-901, Brazil
Fax: + 55 11 3747-1248
E-mail: rkaliks@einstein.br

EDITORIAL COMMENT

The data published by Kaliks et al. (2010) provide additional support for the benefits of adding a pure antiandrogen, in this case flutamide, to patients with metastatic disease showing progression after partial blockade achieved by castration. These results are in agreement with a previous relatively large scale study of 209 metastatic prostate cancer patients showing progression after orchiectomy, treatment with high doses of estrogens or an GnRH agonist alone where the addition of flutamide at the same dose used in the study of Kaliks et al. permitted to achieve complete, partial and stable responses in 6.2%, 9.6% and 18.7% of cases, respectively, for a total clinical benefit of 34.5% (1,2).

Contrary to the opinion that patients in relapse after castration have exclusively "androgen-insensitive" tumors, the above-mentioned data show that "androgen-sensitive tumors are present at all stages of prostate cancer in all patients and that maximal androgen blockade should always be administered with a good possibility of additional response. Instead of being "androgen-insensitive", most of the tumors which continue to grow after castration are androgen-sensitive and able to grow in the presence of the "androgens of adrenal origin left after castration" (1) "Control of their growth requires further androgen blockade" (3).

These results are not surprising since it is now well recognized that following castration alone,

approximately 40% of dihydrotestosterone, the most potent androgen, is left in the prostatic tissue where it continues to stimulate the normal human prostate and prostate cancer (4-8).

It would have been preferable; however, if these patients had not received castration alone, as first treatment, thus leaving 40% of androgens to continue to stimulate their cancer with the high risk of further metastases and the early development of treatment resistance. These patients should have received combined androgen blockade (castration + pure antiandrogen) at start of treatment. Another unfortunate aspect is that cancer was not diagnosed earlier at the clinically localized stage when long-term control and even cure in the majority of cases is a possibility with combined androgen blockade administered as first treatment or immediately following PSA rise upon failure of prostatectomy or radiotherapy (9-11).

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Dr. Fernand Labrie
Research Center, Rm 1743
Laval Univ. Medical Center
2705 Laurier Blvd.
Quebec, PQ G1V 4G2, Canada
E-mail: fernand.labrie@crchul.ulaval.ca

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Safety of Ultrasound-Guided Transrectal Extended Prostate Biopsy in Patients Receiving Low-Dose Aspirin

Ioannis Kariotis, Prodromos Philippou, Demetrios Volanis, Efraim Serafetinides, Demetrios Delakas

Department of Urology, "Asklipieion" General Hospital, Athens, Greece

ABSTRACT

Purpose: To determine whether the peri-procedural administration of low-dose aspirin increases the risk of bleeding complications for patients undergoing extended prostate biopsies.
Materials and Methods: From February 2007 to September 2008, 530 men undergoing extended needle biopsies were divided in two groups; those receiving aspirin and those not receiving aspirin. The morbidity of the procedure, with emphasis on hemorrhagic complications, was assessed prospectively using two standardized questionnaires.
Results: There were no significant differences between the two groups regarding the mean number of biopsy cores (12.9 ± 1.6 vs. 13.1 ± 1.2 cores, p = 0.09). No major biopsy-related complications were noted. Statistical analysis did not demonstrate significant differences in the rate of hematuria (64.5% vs. 60.6%, p = 0.46), rectal bleeding (33.6% vs. 25.9%, p = 0.09) or hemospermia (90.1% vs. 86.9%, p = 0.45). The mean duration of hematuria and rectal bleeding was significantly greater in the aspirin group compared to the control group (4.45 ± 2.7 vs. 2.4 ± 2.6, p = < 0.001 and 3.3 ± 1.3 vs. 1.9 ± 0.7, p < 0.001). Multivariate logistic regression analysis revealed that only younger patients (mean age 60.1 ± 5.8 years) with a lower body mass index (< 25 kg/m^2) receiving aspirin were at a higher risk (odds ratio = 3.46, p = 0.047) for developing hematuria and rectal bleeding after the procedure.
Conclusions: The continuing use of low-dose aspirin in patients undergoing extended prostatic biopsy is a relatively safe option since it does not increase the morbidity of the procedure.

Key words: *prostate; biopsy; transrectal; aspirin*
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INTRODUCTION

Due to the widespread clinical use of prostate specific antigen (PSA) for the early diagnosis of prostate cancer, transrectal ultrasound-guided prostate biopsy has emerged as one of the most frequently performed urological procedures.

Reports published during the last decade have demonstrated that the classical sextant prostate biopsy scheme (as proposed by Hodge in 1989) demonstrates a false negative rate of 19-31% (1). Based on these findings, various biopsy schemes have been proposed, in order to increase the sensitivity of the method. In current clinical practice, 10-core or 12-core biopsy protocols perform better, compared to the sextant scheme, due to their increased sensitivity and relatively low complication rates (2-4).

Older patients constitute the main target group for prostate cancer screening and subsequently undergo prostatic biopsy. At the same time, cardiovascular disease most commonly affects the elderly and low-dose acetylsalicylic acid (ASA, 100 mg,

once daily) is the mainstay of primary and secondary prophylaxis for patients with coronary and peripheral vascular disease.

The optimal management of patients who receive low doses (100 mg) of acetylsalicylic acid (ASA) and who are scheduled to undergo prostatic biopsy is controversial. The approaches being implemented in everyday clinical practice vary and include discontinuation of ASA, replacement of ASA with low-molecular weight heparin and continuing ASA during the peri-procedural period (5,6).

The aim of this study is to determine whether the incidence of hemorrhagic complications after an extended-scheme (12 or more cores) prostatic biopsy is increased for patients who continue to take low-dose ASA compared to patients not receiving ASA.

MATERIALS AND METHODS

The study was approved by the Local Research Ethics Committees. Between February 2007 and September 2008, after written informed consent was received, 530 patients were considered for prostate biopsy and were included in the protocol database. Indications for biopsy included PSA value greater than 2.5 ng/mL and/or an abnormal digital rectal examination. Exclusion criteria included: treatment with coumadin or antiplatelet drugs (clopidogrel, triflusal), a personal history of hemorrhagic diathesis, inflammatory bowel disease, malignancy in other pelvic organs, chronic liver disease, renal failure and concomitant rectal diseases such as polyps, rectal fissures, hemorrhoids and anal strictures.

Biopsy Protocol

All patients received an antibiotic prophylaxis with 150 mg netilmicin intramuscularly before biopsy and 500 mg ciprofloxacin twice a day administered one day before and for 4 days after the biopsy. Patients under ASA treatment were instructed to continue its use before and after the procedure.

A biplanar transrectal probe (Pro-Focus 2202™, B-K Medical, Denmark), with capability of real-time three-dimensional imaging was used. The biopsy needle was 18G in diameter and tissue cores were obtained by using an automated biopsy gun (Pro-Mag™). Intramuscular dextropropoxyphene hydrochloride administered 30 minutes prior to biopsy and local application of lidocaine gel 2% were used for peri-procedural pain control. During transrectal ultrasound scanning of the gland, the anatomic capsule, the posterolateral peripheral zone and the junction of the prostatic base with the seminal vesicles were thoroughly visualized as areas of high incidence of cancer and the presence of hypoechoic regions was noted. All the biopsies were performed by the same consultant urologist. Biopsy protocol included a standard systematic 12-core scheme (6 cores per lobe). Where deemed necessary by ultrasound findings (e.g. specific hypoechoic lesions), more additional targeted biopsies were obtained.

Morbidity Assessment

Two questionnaires were used to assess patient characteristics, clinical and laboratory features and patient- and physician-reported morbidity of the procedure. The first questionnaire was completed by the treating physician after the biopsy and included items such as prostate volume and number of biopsy cores, PSA and free PSA values, body mass index (BMI) calculation and immediate complications. The second questionnaire included questions regarding the late occurrence and duration of hemorrhagic or other complications (urinary retention, fever, etc.) and the need for a doctor's consultation or for hospitalization due to a biopsy-related problem, as well as the overall burden which was imposed on the patient's quality of life. This questionnaire was completed by the patients one month later, during a scheduled re-evaluation, according to the department's policy.

Rectal bleeding was defined as spontaneous or defecation-associated blood loss. Hematuria was graded as mild (intermittent, absence of blood clots, lasting less than 48 hours), moderate (presence of clots and involving more than 50% of voids for two to five days) and severe (acute retention due to clots, need for patient hospitalization). Pain was evaluated by using the 1-10 numeric rating scale (NRS).

Statistical Analysis

Statistical Analysis was done with the SPSS software package (SPSS 13.0 Inc, Chicago, IL). Univariate analyses were performed, using Student's-t-test and Mann-Whitney U test for continuous variables and Chi-square test or Fisher's exact test for categorical variables. A multiple logistic regression model was designed to determine the factors (age, number of biopsy cores, PSA, prostate volume, BMI) associated with hemorrhagic complications. To find the best model, a backward elimination stepwise procedure was carried out so that the factor would be eliminated from the analysis if the corresponding P value was greater than 0.15. A two tailed p value of 0.05 or less was considered statistically significant.

RESULTS

The procedure was interrupted in eight patients due to bradycardia and hypotension, and these patients were excluded from the study. A total of 434 patients fulfilled the inclusion criteria, fully completed the questionnaire and returned for scheduled re-evaluation. Of them, 152 were under ASA treatment on a daily basis and were instructed to continue ASA before and after undergoing the procedure (Aspirin Group), while 282 patients did not receive ASA (Control Group). The most common reason for taking aspirin was primary or secondary prevention of coronary heart disease (48.6%) and the prevention of graft occlusion after coronary artery bypass grafting (11.7%). The mean duration of aspirin therapy was 19.6 ± 11.7 (range 1-43) months.

Demographic and clinical characteristics of the patients were comparable between the two groups (Table-1). The mean number of biopsy cores obtained per patient did not vary significantly between the two groups (12.9 ± 1.6 versus 13.1 ± 1.2 cores, p = 0.09). The histopathology examination revealed the presence of prostate cancer in 149 patients (34.3%). The biopsy was considered well tolerated by the vast majority of patients. The mean score on the NRS was 2.1 and 2.3 for the aspirin and control group, respectively.

Regarding hemorrhagic complication rates, there were no statistically significant differences between the two groups (Table-2). There was no significant difference in the hematuria rate between patients under ASA (64.5%) and patients not taking aspirin (60.6%) (p = 0.46). Rectal bleeding rates (33.5% versus 25.9%, p = 0.09) and hemospermia rates (90.1% versus 86.9%, p = 0.45) were also comparable. Further analysis of hematuria severity, revealed the absence of statistically significant differences; 77.5% of the patients in the Aspirin group and 85.4% of the patients in the Control group reported mild hematuria (p = 0.13), while hematuria was graded as moderate in the remaining 22.5% and 14.6% of the Aspirin and Control groups, respectively (p = 0.13). However, statistically significant differences were noted in terms of duration of bleeding biopsy-related events. The mean duration of hematuria and rectal bleeding was significantly higher in the Aspirin group, compared to the control group. The mean duration of hematuria was 4.45 ± 2.7 and 2.4 ± 2.6 days for the aspirin and

Table 1 – *Demographic and clinical characteristics of patients.*

	Aspirin Group (N = 152)	**Control Group (N = 282)**	**p Value**
Age	65.4	64.3	0.12
BMI (kg/m^2)	28.5	28.1	0.16
Prostate volume (mL)	51	52.1	0.14
Number of cores	12.9	13.1	0.09
PSA (ng/mL)	7.4	7.3	0.23

BMI = body mass index; PSA =prostate specific antigen.

Table 2 – *Incidence and duration of hemorrhagic complications.*

Complications	Aspirin Group	Control Group	p Value
Hematuria	64.5% (98/152)	60.6% (171/282)	0.46
Duration of hematuria (days)	4.45 ± 2.7	2.4 ± 2.6	< 0.001
Severity of hematuria			
Mild	77.5% (76/98)	85.4% (146/171)	0.13
Moderate	22.3% (22/98)	14.6% (25/171)	0.13
Severe	0	0	
Rectal bleeding	33.5% (51/152)	25.9% (73/282)	0.09
Duration of rectal bleeding (days)	3.3 ± 1.3	1.9 ± 0.7	< 0.001
Hemospermia*	90.1% (91/101)	86.9% (159/183)	0.45
Duration of hemospermia	21.2 ± 11.9	22.4 ± 10.4	0.67

Patients who reported intercourse within the first month.

control groups, respectively ($p < 0.001$), while the mean duration of rectal bleeding was 3.3 ± 1.3 and 1.9 ± 0.7 days, respectively ($p < 0.001$). The duration of hemospermia, however, did not vary significantly between the two subsets (21.2 ± 11.9 days and 22.4 ± 10.4 days, respectively, $p = 0.67$).

Further data evaluation with multiple logistic regression analysis, revealed that a specific subgroup of younger patients under ASA (mean age 60.1 ± 5.8 years) with a lower BMI (< 25 kg/m^2) had a higher probability to develop hematuria and/or rectal bleeding, compared to older patients (mean age 70.7 ± 4.2 years) with a higher BMI (> 25 kg/m^2). This difference, however was only marginally statistically significant (odds ratio = 3.46, $p = 0.047$) (Table-3).

The evaluation of overall complication rates also revealed the absence of any significant early or late complications or biopsy-related hospitalizations. Finally, none of the patients reported any significant burden on quality of life because of the biopsy or the post-procedural bleeding complications.

COMMENTS

Ultrasound-guided transrectal biopsy of the prostate is considered nowadays the "gold standard" for the diagnosis of prostate cancer. In everyday clinical practice, it constitutes a relatively safe and well tolerated procedure, performed on an outpatient basis. The most frequent complications observed are hematuria, rectal bleeding and hemospermia. The optimal method for peri procedural pain control has been the topic of many studies. A recent study by Tobias-Machado et al. concluded that periprostatic local anesthesia combined with low-dose sedation

Table 3 – *Multivariate analysis of predictors of bleeding in patients on low-dose aspirin.*

Parameter	Exp (B)	95% CI for Exp (B) Lower-Upper	p Value
PSA	0.878	0.748 - 1.029	0.10
Number of biopsy cores	0.976	0.666 - 1.431	0.90
Prostate volume	0.998	0.968 - 1.033	0.89
Age < 65 years + BMI<25 kg/m^2	3.46	1.017 - 11.817	0.047

Exp (B) = odds ratio; CI = confidence Interval; BMI = body mass index.

provide an effective and safe option (7). We used intramuscular dextropropoxyphene hydrochloride administered 30 minutes prior to biopsy and local application of lidocaine gel 2% with satisfactory pain management.

In this study, the rates of hemorrhagic complications were evaluated using a questionnaire that was completed by the patients one month after the biopsy during a scheduled re-evaluation. In order to diminish recall bias, before discharge, the patients were specifically instructed to be aware of any bleeding complication and to note its duration. Rates of hemorrhagic complications, as reported in prospective studies that included more than 100 patients and 6-12 prostate biopsy cores per patient, vary widely (8-11) (10-74% for hematuria, 1-40% for rectal bleeding and 10-78% for hemospermia). These wide variations can be attributed to different methods for evaluation of complication rates, differences in complication definition, selection bias during the recruitment of patients for the study and patient preoccupation with bleeding complications because of pre-procedural informed consent. Severe and potentially life-threatening complications such as parasympatheticotonia, sepsis and uncontrollable bleeding occur at a rate of 1-2%. These complications, however, can be prevented by detailed history, excellent knowledge of the ultrasonographic anatomy of the prostate and appropriate antibiotic prophylaxis.

Currently, ASA is the antiplatelet agent of choice, due to its relative safety, efficacy and low cost. For most elective surgeries, it has typically been recommended that the patient stop taking ASA 7 to 10 days before the procedure. The optimal management of patients who are scheduled for prostate biopsy and receive ASA is controversial. The lack of solid evidence contributes to the implementation of various or even controversial approaches regarding the management of these patients. Due to the estimation that the number of transrectal prostate biopsies performed is going to increase in the near future, the need for evidence-based recommendations regarding these patients is more than apparent.

On the other hand, there is evidence in recent reports that coronary patients who abruptly discontinue ASA treatment are at increased risk for a new acute vascular event (12). Acute cardiac events are noted within 10 days of ASA withdrawal and are due to coronary thrombosis. There are also clinical and experimental data that the "rebound thrombosis phenomenon" increases cerebrovascular event rates as well (13). These findings support the recommendation to restart ASA treatment within 8-10 days after a major procedure for which ASA withdrawal was deemed necessary. Burger et al. published a meta-analysis in 2005 (14) which highlighted the fact that patients under ASA treatment are exposed to a higher risk of bleeding complications during most procedures, but aspirin does not lead to a higher level of severity of bleeding complications (with the exceptions of intracranial surgery and possibly transurethral prostatectomy). These findings suggest that only patients scheduled for intracranial procedures and transurethral prostatectomy should be exposed to the increased cardiovascular risk associated with ASA withdrawal.

According to our findings, patients who undergo extended prostatic biopsy while on ASA treatment are not at increased risk for bleeding complications, compared to patients not taking ASA. This finding has been noted in previous reports, which however involved less biopsy cores per patient (6-core or 8-core biopsy schemes) (15,16). One other study by Halliwell et al. demonstrated an increased risk of minor but not major bleeding complications in patients taking ASA (17). The relatively low incidence of hemorrhagic events can be attributed to the phenomenon of individual patient resistance to ASA in low (100 mg) doses, which results in treatment failure in up to 30% of patients (18,19). In addition, ASA is considered an antiplatelet agent of low potency, leading to the recommendation for combining ASA with a second antiplatelet agent, such as clopidogrel, for patients at high risk for cardiovascular events (20). In our study, an interesting finding was that patients of younger age (< 65 years) and lower BMI (< 25 kg/m^2) had a higher probability for having bleeding, as opposed to older patients (> 70 years) with higher BMI (> 25 kg/m^2). This difference, however, was statistically marginal. Several reports suggested that older and obese patients are more prone to the development of aspirin resistance (21, 22). One can suggest that ASA antiplatelet effect is more pronounced in younger patients with lower BMI or that the optimal dose of ASA is BMI-dependent.

CONCLUSION

Continued low-dose ASA treatment is not associated with an increased incidence of hemorrhagic complications after an extended (12 or more cores) prostatic biopsy and therefore ASA withdrawal is not considered justified. Prospective randomized trials are needed, in order to provide solid data for evidence-based recommendations.

CONFLICT OF INTEREST

None declared.

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Correspondence address:
Dr. Demetrios Delakas
Department of Urology
Asklipieion General Hospital
1, Vasileos Pavlou Avenue
16673, Voula, Athens, Greece
Fax: + 30 210 892-3111
E-mail: delakas@mail.gr

EDITORIAL COMMENT

The present study suggest that the continued use of low-dose aspirin (LDA) in patients undergoing TRUS-guided prostate biopsy does not increase the incidence of mild bleeding complications, it only prolongs the duration of self-limited hematuria and rectal bleeding.

This study was not devoid of limitations. First, most patients take LDA as a prophylactic agent for coronary and peripheral vascular diseases and a control group of patients with discontinuing LDA was necessary to compare patients with the same comorbities. Second, the question of whether the longer duration of hematuria and rectal bleeding in men who continued LDA is clinically significant might have been addressed by a comparison of the hemoglobin levels before and after prostate biopsy. Third, the duration of hematospermia, which can persist for up to 2 months after prostate biopsy, was not recorded after 30 days (1).

There are no guidelines on the management of LDA before taking prostate biopsies but there appears to be no strong scientific evidence for the withdrawal of aspirin in all patients undergoing prostate biopsy.

In one study, 52% of radiologists and 27% of urologists terminated aspirin before prostate biopsy (2). In the UK, 35% of urologists routinely stop aspirin before prostate biopsy (3).

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Dr. Valdemar Ortiz
Chair, Section of Urology
Federal University of Sao Paulo, UNIFESP
Sao Paulo, SP, Brazil
E-mail: valdor@uol.com.br

EDITORIAL COMMENT

Although prostate biopsy is widespread and regarded as a routine office procedure, some men are probably harmed. Kariotis et al. (1) evaluated whether the continuing use of low-dose aspirin in patients undergoing extended prostate biopsy is a safe option. The authors should be congratulated for the clarity of the text, the excellent analysis, and the cautious interpretation of their results.

The goals of prostate biopsy are to avoid biopsy-associated complications such as bleeding, infection and pain as well as to detect prostate cancer effectively. Especially, patient safety is a worldwide concern. Every medical and surgical interventions have benefits and risks. Patients and physicians deserve to be fully informed about the risks as well as benefits.

The use of aspirin was already found to be a relatively safe option in patients undergoing extended prostate biopsy (2-6). However, some investigators reported that aspirin prolonged the duration of hematuria and rectal bleeding (7) or exacerbated minor bleeding complications (8). Therefore, to confirm whether patients taking aspirin were more likely to experience bleeding complications in routine clinical setting, as admitted by the authors, prospective randomized studies should be designed.

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Dr. Jae-Seung Paick
Department of Urology
Seoul National University Hospital
Seoul, Korea
E-mail: jspaick@snu.ac.kr

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Monti's Procedure as an Alternative Technique in Complex Urethral Distraction Defect

Jalil Hosseini, Ali Kaviani, Mohammad M. Mazloomfard, Ali R. Golshan

Reconstructive Urology, Shohada Tajrish Hospital, Shaheed Beheshti Medical Sciences University, Tehran, Iran

ABSTRACT

Purpose: Pelvic fracture urethral distraction defect is usually managed by the end to end anastomotic urethroplasty. Surgical repair of those patients with post-traumatic complex posterior urethral defects, who have undergone failed previous surgical treatments, remains one of the most challenging problems in urology. Appendix urinary diversion could be used in such cases. However, the appendix tissue is not always usable. We report our experience on management of patients with long urethral defect with history of one or more failed urethroplasties by Monti channel urinary diversion.
Materials and Methods: From 2001 to 2007, we evaluated data from 8 male patients aged 28 to 76 years (mean age 42.5) in whom the Monti technique was performed. All cases had history of posterior urethral defect with one or more failed procedures for urethral reconstruction including urethroplasty. A 2 to 2.5 cm segment of ileum, which had a suitable blood supply, was cut. After the re-anastomosis of the ileum, we closed the opened ileum transversely surrounding a 14-16 Fr urethral catheter using running Vicryl sutures. The newly built tube was used as an appendix during diversion.
Results: All patients performed catheterization through the conduit without difficulty and stomal stenosis. Mild stomal incontinence occurred in one patient in the supine position who became continent after adjustment of the catheterization intervals. There was no dehiscence, necrosis or perforation of the tube.
Conclusion: Based on our data, Monti's procedure seems to be a valuable technique in patients with very long complicated urethral defect who cannot be managed with routine urethroplastic techniques.

Key words: *urethra; urethral stricture; urinary diversion*
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INTRODUCTION

Strictures and defects of the posterior urethra in men is one of the most significant clinical complications concerning urologists (1). Posterior urethral injuries in pelvic fracture were estimated at 5 to 10 percent in previous studies (2). Anastomosis is usually performed for defects of the posterior urethra. However, in some cases the urethral defect is so long that it cannot be negotiated with vigorous releasing of urethra from surrounding tissue, inferior pubectomy and even re-routing maneuvers (1,3). Based on the location and length of the stricture, various techniques have been used in such cases including onlay repairs, stricture excision with augmented anastomosis, a tubularized flap of sigmoid colon, and free or vascularized skin flap, etc. However, many complications have been related to these techniques (4,5). Other options such as perineostomy or suprapubic tube could also be used as salvage procedure (6,7). Application of appendix tissue for the creation of a catheterizable stoma remains a useful technique in patients with

more severe urethral injuries (8); although, the appendix is not always usable (9). The appendix may be absent or insufficient in length or quality. It may have a precarious blood supply, a short mesentery or histopathologic changes, such as chronic inflammation or fibrous lumen obstruction (9). Regarding these situations, the technique which was originally proposed by Monti et al. is a good alternative method when the appendix is unavailable, atretic or used concurrently with another procedure (10). We reviewed our results regarding this surgical technique in eligible patients.

MATERIALS AND METHODS

From 2001 to 2007, we evaluated data from 8 male patients aged 28 to 76 years (mean age 42.5) on whom we performed the Monti technique at Tajrish Hospital, Tehran, Iran. All patients had a previous history of urethral distraction defect and a history of at least one failed urethroplasty and a defect longer than 10 centimeters in distal prostatic, membranous, bulbar and some part of penile urethra. Due to a very long urethral defect that could not be repaired by urethroplasty, a Monti urinary diversion was performed in the patients. Informed consents were signed by all enrolled patients. The study was approved by the Ethics Committee of our hospital.

Surgical Technique

After isolating a 2 to 2.5 cm segment of ileum, with a suitable blood supply, we opened the ileal segment along its anti-mesenteric border by Metzenbaum scissors, and then closed the opened ileum transversely surrounding a 14-16 Fr urethral catheter using running Vicryl sutures (Figure-1). The length of small intestine which was resected did not determine the length of the newly built tube, but rather its diameter. Therefore, using 1 or 2 cm segment of the small intestine, leads to a narrow and wide tube, respectively. The 15 cm of terminal ileum was not routinely used for this type of procedure.

The double tube technique was used in obese patients. In this procedure, a 5 cm segment of the ileum was isolated, cut into two halves and tabularized, each one exactly as described previously. The two segments were anastomosed to each other using an interrupted 3-0 Vicryl sutures to build a single tube.

After the reconstruction of a new appendix, anastomosis was performed on the superior part of the postero-lateral junction of the bladder. The Mitrofanoff principle was not used; the bladder wall was opened and anastomosed to the new appendix using 3-0 Vicryl sutures (Figure-2). The stoma was made at level which was located proximally relative to the bladder in order that gravity can help the patient's continence. A cystostomy tube was performed for all the patients to increase the safety measures.

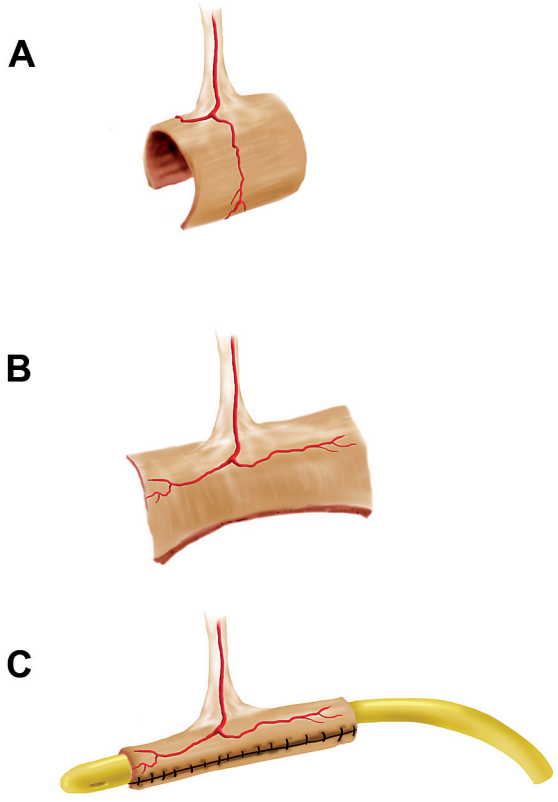

Figure 1 *– Isolating a 2 to 2.5 cm segment of ileum (A) and opening it from its anti-mesenteric border (B) and finally retubularization along its longitudinal axis (C).*

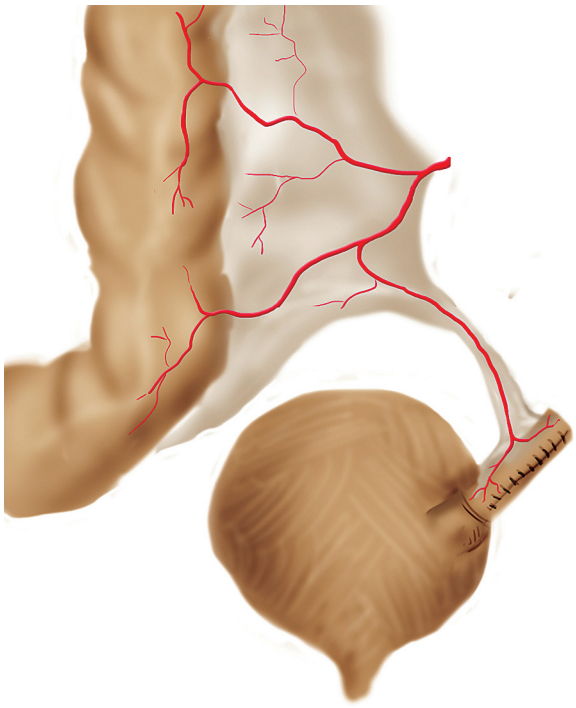

Figure 2 *– Anastomosis of newly build tube on the superior part of the postero-lateral junction of the bladder.*

All patients were discharged 5-6 days postoperatively as soon as they could tolerate solid food. The diversion catheter was removed 3 weeks post-operatively. All patients were put on a clean intermittent catheterization (CIC) regimen using a 14 or 16 Fr nelaton catheter every 3 hours. Presence of urinary leakage during the interval was considered as the patient being incontinent. The cystostomy tube was removed 7 days later, if there was no difficulty in catheterization.

Demographic characteristics, distraction defect length, previous surgical procedures, time of operation and hospitalization, estimated blood loss, and complications such as peri-operative bleeding (need for blood transfusion), adjacent organ damage, hematoma and wound infection were recorded.

The patients were regularly followed-up at 3,6,18 and 24 months postoperatively, with special attention to any problems with catheterization and incontinence. Follow-up plan consisted of physical examination including stoma evaluation; upper urinary tract sonography and determining of post catheterization urine residue; and serum creatinine level and catheter size assessment.

RESULTS

Eight patients were included in this study. Causes of urethral injury and pelvic fracture consisted of 4 motor vehicle accidents, 2 falls and one shot gun injury. The time interval between injury and Monti procedure ranged from 23 to 48 months (mean 31.4). Patients' general data, previous operative procedures and outcome are listed in Table-1. Sonographic assessment of upper urinary tract did not reveal any pathologic findings, and mean serum creatinine level was 1.3 mg/dL (0.6 to 1.7) pre-operatively. The patients did not have an available or suitable appendix (Table-2).

Seven patients underwent single tube technique and in the obese patient, double tube procedure was performed. Mean surgical time was 4.5 hours (range 3 to 8) with defect lengths of 11.75 cm (10 to 14). Average estimated blood loss was around 350 cc (ranged 200 to 800). There was no need for blood transfusion or adjacent organ damage. All patients were discharged 5-6 days post operatively.

Follow-up ranged from 24 to 30 months (mean 25.75). Immediate post-operative complications such as hematoma and wound infection were not detected. All patients performed catheterization through the conduit without difficulty every 3 hours. Catheter size ranged from 14 to 16 Fr. None of the 8 patients had stomal stenosis during the follow-up period. Mild stomal incontinence occurred in one patient in the supine position which became continent after some adjustments of the catheterization intervals. This patient had previous history of urethroplasty and failed appendicovesicostomy at another surgical center. There was no dehiscence, necrosis, or perforation of the tube during the follow-up period.

Also, there was no significant difference between pre-operative and post-operative serum creatinine levels and upper tract sonographic data, which were evaluated at the time of scheduled surgery as well as 3,6,18 and 24 months post-operatively.

Table 1 *– Patients' general data, operative procedures and outcome.*

Patient	Age (years)	Defect Length (cm)	Cause of Injury	Previous Urethral Intervention	Time from Injury to Operation (months)	Follow-up Duration (months)	Outcome
1	28	10	Penetrating injury (Shot gun)	Laparotomy and cystostomy; RUF resection with U; Several IU	25	24	No residual; No stenosis
2	32	12	Motor vehicle injury with pelvic fracture	Laparotomy and cystostomy; Once U	35	25	No residual; No stenosis
3	56	10	Falling down injury with pelvic fracture	Twice U; Several IU	36	26	No residual; No stenosis
4*	31	14	Motor vehicle injury with pelvic fracture	Laparotomy and cystostomy; Once U	23	29	No residual; No stenosis
5	76	13	Falling down injury with pelvic fracture	Laparotomy and cystostomy; Once U; Failed AV	48	30	Variable residual; No stenosis; Mild incontinence
6	29	12	Motor vehicle injury with pelvic fracture	Once U; Several IU	28	24	No residual; No stenosis
7	40	11	Motor vehicle injury with pelvic fracture	Laparotomy and cystostomy; Once U;	24	24	No residual; No stenosis
8	48	12	Motor vehicle injury with pelvic fracture	Laparotomy and cystostomy; Once U; Several IU	32	24	No residual; No stenosis

** The only double Monti channel; RUF = recto-urethral fistula; U = urethroplasty; IU = internal urethrotomy; AV = appendicovesicostomy.*

COMMENTS

In 1989 Turner-Warwick explained some features of complex urethral distraction defect including long urethral gap between tow ends (11). In severe urethral injuries with long strictures or urethral defects especially in patients who have undergone failed previous surgical treatments, various methods have been used to obtain urethral continuity (4). Surgical options are offered based on the location and length of the stricture. One-stage vascularized scrotal skin flap urethroplasty and a two-stage Johanson's procedure

***Table 2** – Causes of unavailability of appendix.*

Condition	Number (%)
Appendectomy	4 (50)
Insufficient length*	2 (25)
Fibrous lumen obstruction*	1 (12.5)
Failed appendicovesicostomy	1 (12.5)
Total	8 (100)

** Finding on operation room.*

were two surgical examples for treatment of complex lengthy urethral strictures (12). Skin flap urethroplasty can lead to some complications such as recurrent stricture, troublesome post void dribbling, and diverticulum formation (4). In the last decade, buccal mucosa urethroplasty has increased in popularity because of its feasibility, good functional outcome, and low morbidity at the reconstructed urethra. However, treatment of long, complicated urethral strictures by buccal mucosal graft may not be useful, because of limited material (4,5).

Recently some investigators have described novel surgical techniques for male long segment urethral defect. In 2006, Yue-Min Xu et al. reported a new technique for treatment of men with long urethral defect after pelvic trauma using the intact and pedicled pendulous urethra to replace the bulbar and membranous urethra, followed by reconstruction of the anterior urethra (12). Buyukunal et al. developed a new treatment modality in a rabbit model, using appendix interposition for substitution of severe posterior urethral injuries (13). This technique was also used by Aggarwal et al. in recurrent urethral strictures (14).

Other options such as perineostomy or suprapubic tube could also be used as a salvage procedure in such situations. Suprapubic tube is a safe and simple treatment of acute or chronic urinary retention but has some complications especially in long-term such as infection, difficulty in changing of catheter and risk of malignancy (6). Barbagli et al. evaluated the clinical outcome of patients with complex urethral pathology who were treated with perineal urethrostomy. These authors showed that success rate of urethroplasty after perineal urethrostomy is lower in younger patients with traumatic urethral stricture (7).

In 1980, Mitrofanoff first described the use of the appendix as a continent urinary stoma (15). The major indications for constructing a urinary diversion are patients with a low leak-point pressure and neurogenic bladder, an unreconstructable bladder (e.g. exstrophy), an unreconstructable urethral disease or the inability to catheterize the urethra in a neurogenic bladder (8).

With this concern, we use a urinary diversion in patients with unreconstructable long urethral defect, in order to empty their bladder. As Monti et al. described in 1997 (10), a continent catheterizable conduit using short segments of the small intestine was used for this aim. The use of this technique allows us to obtain some benefits. Only 2 to 2.5 cm segment of the ileum is required. The caliber of such a tube allows catheterization with a 16F to 18F catheter, and the mucosal folds of the ileum are aligned with its longitudinal axis. These tubes have an abundant supply of blood and are able to be used anywhere inside the abdomen (9,10).

It is important to note that the length of the segment can be adjusted by using a double tube or using a section of the large bowel, allowing application of this technique in adults or obese patients (9). A 2.0-2.5 cm segment of bowel will usually result in a tube of 6-7 cm in length, when re-tubularized transversely. If a longer channel is needed, two consecutive segments can be cut, and anastomosed together to form a tube twice as long but with mesentery only in the central portion of the tube. In our study, one patient was candidate for the double tube technique. No stenosis or incontinence occurred during his follow-up.

One of the best characteristics provided by Monti's procedure is urinary continence. In the series with longer follow-up periods, continence maintenance is always greater than 90% and shows no considerable changes with time (16,17). Narayanaswamy et al. reported their results with 94 Mitrofanoff procedures, of which 25 were Monti channels. Overall 23 of 25 patients were successfully catheterized at the time of the report and only 3 of 25 had stomal leakage (18). In another large series Castellan et al. reported a comparison among different types of channels for urinary and fecal incontinence, including 45 Monti urinary channels, with a mean follow-up of 38 months.

Four of these channels were double Monti channels, while the others were single Monti channels. Channel replacement was performed in three patients (7%) due to complete fibrosis, and 3 cases (7%) had stomal incontinence (16).

We did not use the Mitrofanoff principle to create an anti-incontinent submucosal tunnel. Only anastomosis was performed on the superior part of the postero-lateral junction of the bladder. Yang et al. (19) evaluated the pressure profile of the channel tube, and detected two high-pressure zones: one in the sub mucosal tunnel and the other at the point at which the muscle layer of the abdominal wall is crossed. These data suggest that the muscle layer of the abdominal wall is a major factor in preserving of continence (9).

Our study shows that Monti's procedure, even without the use of the Mitrofanoff principle, is a reliable technique with low incontinence and stricture rate. Obviously, we are not proposing that the Monti's procedure be the definitive treatment for complicated posterior urethral injuries. Moreover, it can be performed in patients with very long urethral stricture that cannot be corrected with the urethroplastic techniques, and who also do not have a suitable appendix for appendix diversion techniques. However, evaluation of patient's satisfaction and the choice of eligible cases need more investigations with larger number of patients.

CONCLUSION

Based on our data, Monti's procedure is a valuable technique in patients with very long complicated urethral defect who lack a suitable appendix for appendicovesicostomy technique.

CONFLICT OF INTEREST

None declared.

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Correspondence Address:
Dr. Mohammad Mohsen Mazloomfard
Shohada Tajrish Hospital
Shaheed Beheshti Medical Sciences University
Tehran, Iran
Fax: + 98 21 8852-6901
E-mail: mazloomfard@yahoo.com

EDITORIAL COMMENT

The authors report their experience on the management of eight patients with long urethral defects already submitted to at least one unsuccessful urethroplasty. All of them received continent cutaneous urinary diversion using as efferent catheterizable conduit transversely tubularized ileal segments with direct implantation into the bladder wall without antireflux technique. After two years of minimum follow up all subjects were continent with easy catheterization. The ileal tube was created to replace the appendix when unavailable to construct a urinary diversion based on the Mitrofanoff principle. Until that the proposed technical alternatives (around 20) showed clearly inferior results compared to the appendix technique and were based on the use of ureteral segments, longitudinally tapered ileal segments, gastric tubes, tubularized cecum flaps, fallopian tube, skin tubes (preputial penile or clitoral skin flaps, labia minora flaps), vas deferens, tubularized bladder flap, Meckel's diverticulum, hipogastric artery segment, human umbilical vein, rectus abdominis muscle, aponeurosis flap. The long term follow up of ileal tube technique application provided equivalent results to those of the appendix related to function, durability and low complications index (1,2). For the tube construction, some technical points matter. The tube made from 2.5 cm isolated segment allows 14F to 16F catheters inside and the measurement should be performed with the bowel at rest, without stretching it. The tubularization is done with running suture of Vicryl 3-0 in adults and 4-0 in children and preceded by resection of lateral mucosal excess of the open intestinal plate. In the case of double tube, the suture between the plates should be done with simple interrupted stitch, which makes the tubularization easier. You can also use the double spiral tube, as proposed by Casale (3). The passage of the tube to the skin should be straight and as short as possible. Very long tubes evolve with greater difficulty in catheterization. The reservoir must be fixed to the abdominal wall with

vicryl 3-0 interrupted stitch to stabilize the structure. The stoma can be done in a simple way or with skin flaps interposition. It is noteworthy the author's option for direct implantation of the tube into the bladder wall trusting just in the resistance offered by the abdominal muscle layer when the tube pass through it. Since the Mitrofanoff's pioneer publication in 1980 (reference 15) there were rare descriptions of direct implantation of the conduit into the reservoir without antireflux technique and with short periods of continence. Yang himself quoted by the authors (reference 19 in the article) utilized the antireflux technique in his unique case with ileal tube and interprets literally the pressure profile study of the tube: "The results show that although there are 2 high pressure profile zones for the continent ileal tube, the skeletal muscle pressure zone has a lesser role in the continence mechanism than the submucosal portion of the ileal tube". Stress tests show an equal increased pressure inside the reservoir and in the antireflux tunnel but not in the skeletal muscle zone. This conclusion is the current stand-point and it seems risky to dismiss the use of an antireflux technique mainly in cases in which the tube implantation was done into the bladder wall, a structure that offers the best results among the available options. Long term studies show that the continent cutaneous urinary diversion made by the Mitrofanoff technique with appendix or reconfigured ileal tube offers consistent and lasting results besides the use of technical principles of easier execution already widely known and used in Urology.

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Dr. Paulo R. Monti
Section of Urology
Federal University of Minas Triangle
Uberaba, Minas Gerais, Brazil
E-mail: montipr@zaz.com.br

EDITORIAL COMMENT

Traumatic posterior urethral strictures (better defined as "pelvic fracture related urethral injuries") as well as non-traumatic posterior strictures are rare conditions (1,2). As mentioned by the authors, most of these strictures can be managed by anastomotic repair. However, reports on "what to do" after failed urethroplasty are very scarce. The Monti-procedure was first described in 1997 (3) in an animal (dog) model and quickly found clinical applications as a continent catheterizable stoma in adult and paediatric patients (4), in case the appendix could not been used. This paper is the first to describe this technique for posterior urethral strictures after failed urethral reconstruction. The major importance of this paper is that it shows the feasibility of the procedure in these situations. Although it is explained in the text, the title is somewhat misleading. Monti's procedure must not be regarded as an alternative to other procedures (such as anastomotic repair, substitution urethroplasty, perineostomy) in complex urethral distraction defects. One or even more attempts to restore urethral continuity must always be performed for these often young patients. If these attempts failed however, a strategy that abandons the urethral outlet can be proposed. For this reason, I prefer the term "salvage procedure"

rather than the term "an alternative technique" for the Monti's procedure in these patients. The authors did not apply the Mitrofanoff principle for implantation at the bladder. One patient out of 8 suffered from stomal incontinence. The authors state that this technique has thus a low continence rate. However, this conclusion is drawn on a small number of patients. Unless larger series can prove the opposite, there is at the present no reason to abandon the Mitrofanoff principle for prevention of stomal incontinence. Patients must also be informed about the long-term complications related to the Monti's procedure difficult catheterisation, stomal stenosis and incontinence and it has been reported that 23-27.5% will need revision surgery at the Monti's tube (5,6). There is no reason to assume that these complication and revision rate will be different in patients with traumatic urethral distraction defects.

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Dr. Nicolaas Lumen
Department of Urology
Ghent University Hospital
Ghent, Belgium
E-mail: nicolaas.lumen@ugent.be

EDITORIAL COMMENT

In his commentary, recently, Barbagli underlined that the management of posterior urethral strictures, in patients after pelvic fracture urethral distraction defects (PFUDD), has evolved over time (1). Forty, thirty years ago, in the '70s and the '80s, the transpubic urethroplasty was considered the gold standard in the majority of adults and children suffering from PFUDD. Since '90s, thank to Webster and Ramon's work, an elaborated perineal approach to the posterior urethra was suggested (2). It used ancillary maneuvers, such as separation of the corporeal body, inferior pubectomy and retrocrural urethral rerouting, in order to reduce the gap between the bulbar urethra and the prostatic apex, to remove scar tissue and to perform a tension-free anastomosis.

The management of failed posterior urethroplasty after PFUDD remains challenging and its surgery demanding. In this issue of International Brazil Journal of Urology, Hosseini et al. reported their experience on the treatment of adult patients with complex urethral defect after one or more failed posterior urethroplasties using the Monti channel urinary diversion. The paper is worth reading as it reports data in adult population, although the Monti

procedure is generally used in children. The reader should be aware that failed posterior urethroplasty, in adults, may require urinary diversion just like in primary reconstructive surgery for children. Adults and children are two different populations. In children, PFUDD may evolve into complex urethral strictures because it involves a not-yet-developed proximal urethra (prostatic tract and bladder neck) as well as rudimentary gland and pubo-prostatic ligaments (3,4). Furthermore, prepubescent boys may have insufficient vascular connections in the glans, which is smaller than in adults, resulting in inadequate retrograde blood flow to the distally-based bulbar urethral flap (as a result of bulbar urethral transection and full mobilization). This compromises retrograde blood flow to the anastomotic site may explain the lower success rate of anastomotic urethroplasty in prepubescent boys compared to the adult population (5).

Recently, we compared the spectrum of posterior urethral strictures following PFUDD in developing countries and in Western countries, in order to evaluate if the differences in etiopathogenesis and early treatment of PUFDD might influence the outcome (6). We found remarkable differences in pathogenesis and early treatment of patients with PFUDD. In developing countries, the majority of patients with PFUDD developed an obliterative complex posterior stricture as a consequence of a more serious trauma and delayed primary treatment, which was done by the general surgeon. Hosseini et al.'s paper could confirm this suggestion and it pushes us to reflect upon the following matter. Due to increasing migration rates, the urologists, working in Western countries, will most likely once again encounter the forgotten complicated posterior urethral strictures after PFUDD, in the migrants who have been previously managed in their original country that may require complex perineal/transpubic access or urinary diversion. The implications are evident. Surgical training for urethral reconstruction surgery should be done within international approved surgical training programs which deal with complex, challenging and forgotten situations such those Hosseini and colleagues described and treated in their work.

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Dr. Massimo Lazzeri
Department of Urology
Santa Chiara Hospital
Florence, Italy
E-mail: lazzeri.m@tiscali.it

Dr. Guido Barbagli
Center for Reconstructive Urethral Surgery
Arezzo, Italy

Surgical Technique

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Hand-Assisted Laparoscopic Radical Nephrectomy in the Treatment of a Renal Cell Carcinoma with a Level II Vena Cava Thrombus

Jason R. Kovac, Patrick P. Luke

McMaster Institute of Urology (JRK), St. Joseph's Hospital, Hamilton, Ontario, Canada and Division of Urology (PPL), The University of Western Ontario, London, Ontario, Canada

ABSTRACT

Excision of renal cell carcinoma (RCC) with corresponding vena cava thrombus is a technical challenge requiring open resection and vascular clamping. A 58 year old male with a right kidney tumor presented with a thrombus extending 1 cm into the vena cava. Using a hand-assisted transperitoneal approach through a 7 cm gel-port, the right kidney was dissected and the multiple vascular collaterals supplying the tumor were identified and isolated. The inferior vena cava was mobilized 4 cm cephalad and 4 cm caudal to the right renal vein. Lateral manual traction was applied to the right kidney allowing the tumor thrombus to be retracted into the renal vein, clear of the vena cava. After laparoscopic ultrasonographic confirmation of the location of the tip of the tumor thrombus, an articulating laparoscopic vascular stapler was used to staple the vena cava at the ostium of the right renal vein. This allowed removal of the tumor thrombus without the need for a Satinsky clamp. The surgery was completed in 243 minutes with no intra-operative complications. The entire kidney and tumor thrombus was removed with negative surgical margins. Estimated blood loss was 300 cc. We present a laparoscopic resection of a renal mass with associated level II thrombus using a hand-assisted approach. In patients with minimal caval involvement, our surgical approach presents an option to the traditional open resection of a renal mass.

Key words: *laparoscopy; renal cell carcinoma; nephrectomy; vena cava; thrombus*
Int Braz J Urol. 2010; 36: 327-31

INTRODUCTION

Laparoscopic radical nephrectomy has emerged as a standard surgical option for the treatment of renal cell carcinoma within the past 10 years. First described by Clayman et al. in 1991 (1), laparoscopic radical nephrectomy is associated with reduced post-operative pain and improved convalescence vs. open radical nephrectomy (2). Furthermore, long-term studies have demonstrated similar oncologic outcomes with standard open radical nephrectomy (3).

Involvement of the inferior vena cava (IVC) occurs in 4-10% of renal cell carcinoma (RCC) patients (4). The presence of a renal vein thrombus was previously considered a contraindication to laparoscopic resection. The first case-report description of a laparoscopic nephrectomy with the thrombus extending into the renal vein (level I) was by Savage et al. in 2000 (5). Subsequently, the technical feasibility of this approach was confirmed by our group and others (6,7).

Extension of the thrombus into the vena cava (level II) complicates the laparoscopic approach.

Using a porcine model, Fergany et al. (8) reported 7 successful nephrectomies with level II caval thrombi. Others have expanded these animal studies to clinical cases with thrombi projecting 1 cm (9) and 2 cm (10) into the vena cava. In those studies, Satinsky vascular clamps were used to achieve control of the cava and required laparoscopic vascular suturing experience (11,12).

In this report, we describe a 58 year-old male presenting with an 8x9 cm RCC and metastatic lung nodules. A 1 cm level II vena cava thrombus was identified and removed using a hand-assisted laparoscopic (HAL) approach. The described approach obviates the need for laparoscopic vascular suturing.

SURGICAL TECHNIQUE

A 58 year old male with 20 pack-year smoking history presented with gross hematuria. Ultrasound documented a mass in the upper pole of the right kidney. This was confirmed by computerized tomography (CT) scan to be an 8x9 cm soft tissue mass in the right kidney (Figure-1). This also demonstrated a tumor thrombus projecting 1 cm into the IVC. Right hilar lymphadenopathy and four metastatic, subpleural lung nodules were also seen. A bone scan revealed no evidence of bony metastatic disease.

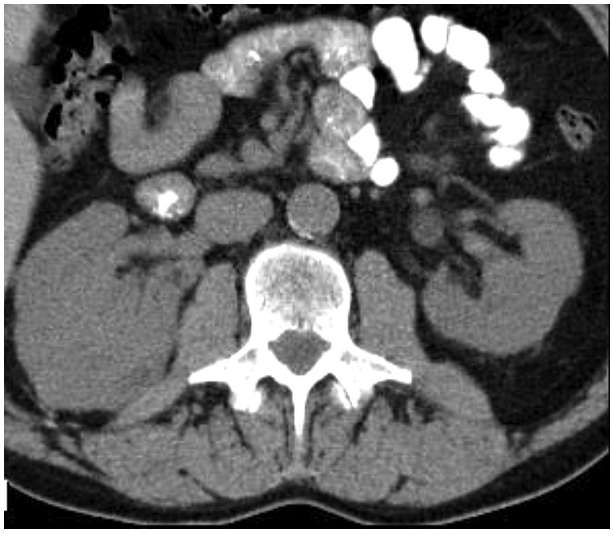

Figure 1 *– The renal mass was confirmed to be 8x9 cm in size with a thrombus present in the right renal vein extending approximately 1 cm into the vena cava.*

After discussion of its risks and potential survival benefit (13,14), cytoreductive nephrectomy was performed. The authors were prepared to perform a laparoscopic hand assisted nephrectomy with vascular control through a Gel Port® (Applied Medical, Rancho Santa Margarita, California). Satinsky clamps were to be used in the thrombectomy and laparoscopic suturing of the cava. After induction with general anesthesia, the patient was positioned in the left lateral decubitus position. With a muscle splitting incision, a 7 cm laparoscopic hand-assist device was placed in the right lower quadrant with the placement of two additional 10 mm ports directly cephalad along the lateral rectus border, allowing 8 cm separation between the ports and the hand-assist device.

Following dissection into the retroperitoneal space, the kidney was separated from the psoas muscle, adjacent bowel and liver. The ureter and multiple vascular collaterals were carefully isolated and divided. The renal artery was controlled with laparoscopic clips and divided, thereby isolating the entire right kidney, excluding the right renal vein. The renal vein was dissected and the location of the tumor thrombus identified through palpation. Intraoperative Doppler ultrasound was used to identify the tip of the tumor thrombus and to exclude the presence of thrombus within the cava. The lateral cava was extensively dissected around the entire right renal vein. Furthermore, the IVC around the right renal vein was dissected posteriorly and medially to permit mobilization of the cava from retroperitoneal attachments over a vertical distance of 8 cm. To remove the renal vein and adjacent caval thrombus, gentle lateral traction was applied to the kidney (Figure-2). Surprisingly, this maneuver allowed the tumor thrombus to retract back within the renal vein. The position of the tumor thrombus was confirmed with intra-operative Doppler ultrasound. With the cava bowed laterally, the cava was stapled at the junction of the right renal vein and cava using a 45 mm articulating vascular stapler (Ethicon Endosurgery, CA). Through palpation and visual inspection, there was no evidence of significant narrowing of the cava from its original capacity. The specimen was extracted and the entire tumor thrombus was examined and shown to be intact. Importantly, the

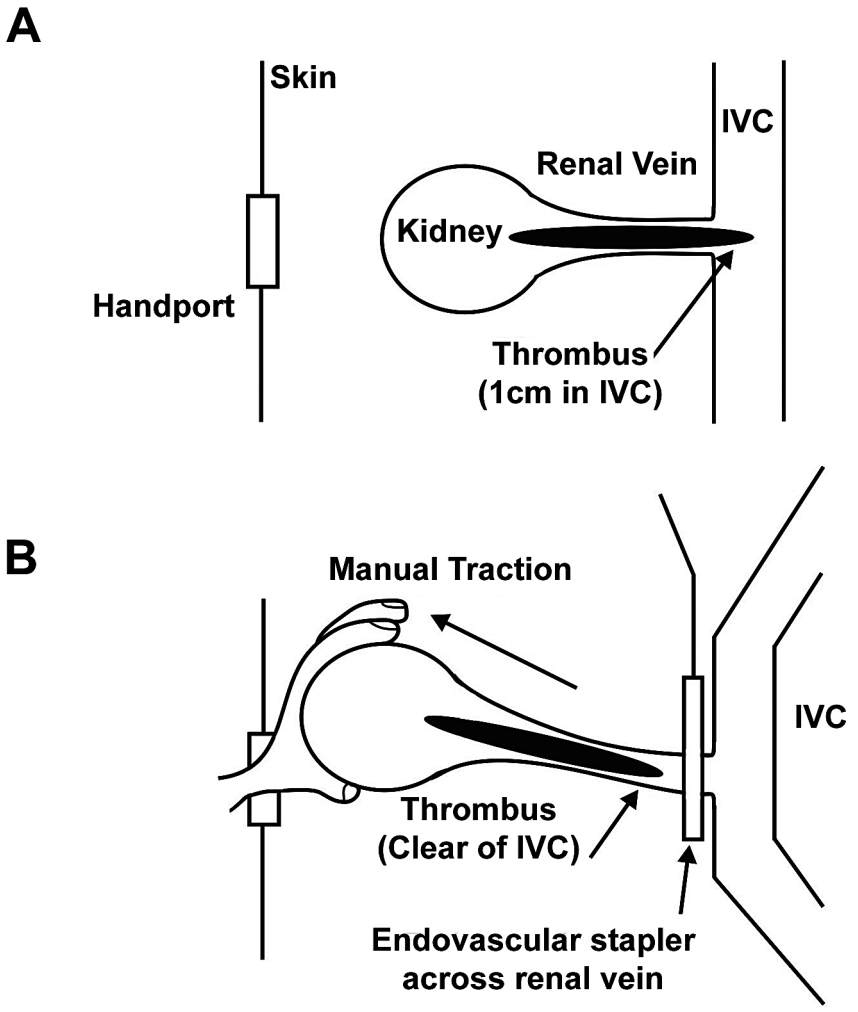

Figure 2 – *A schematic illustration demonstrating the technique employed to free the thrombus from the vena cava. The surgeons hand was introduced into the operative field through a 7 cm gel-port. Following dissection, gentle manual traction was applied to the kidney. Mobilization of the inferior vena cava (IVC) allowed the thrombus to retract into the renal vein. Palpation confirmed that the tumor thrombus was clear of the IVC. An articulating 45 mm endovascular stapler was then used to separate the renal vein from the IVC.*

thrombus was clear of the staple line. The operation concluded in the standard fashion.

The procedure was completed successfully with a surgical time of 3.5 hr and an estimated blood loss of 300 mL. Patient controlled analgesia with morphine was discontinued on post-operative day one. Post-operatively, the patient developed a mild ileus. A CT scan to investigate the ileus demonstrated subclinical pulmonary emboli noted at the lung bases. Anticoagulation was performed and the patient was treated with temsirolimus (mTOR inhibitor) therapy for his metastatic disease. Pathology revealed the tumor to be a clear cell carcinoma (Fuhrman grade 4) with tumor invasion into the perinephric fat and negative resection margins. Twelve months post-operatively, the metastatic deposits remained stable and the emboli resolved on follow-up thoracic CT scanning.

COMMENTS

Excision of a RCC with a level II caval thrombus is a technical challenge. Open radical nephrectomy is the current standard of treatment, however successful laparoscopic removal of tumors with level I renal vein thrombus (6) has opened the door to resection of more extensive tumors.

Our group has previously reported that laparoscopic resection of renal tumors with level I renal vein thrombi is feasible with and without the use of laparoscopic ultrasound and hand assistance (6). Accordingly, the Doppler ultrasound can distinguish the location of the tip of the tumor thrombus, thereby providing a safe window through which the laparoscopic stapler can be applied. Hand assistance devices also permit the use of tactile assessment of the tip of the tumor thrombus.

We had originally planned to resect the kidney with tumor thrombus by isolating the tumor thrombus and ostium of the right renal vein using a conventional Satinsky clamp placed through the hand-assist device. However, it was noted that the tumor thrombus could be retracted back flush to the ostium of the right renal vein using lateral traction on the kidney after complete mobilization of the IVC around the level of the renal vein. Doppler ultrasound inspection and tactile assessment confirmed that the tip of the tumor thrombus sat within the confines of the renal vein. This allowed the laparoscopic stapler to be used to achieve vascular control instead of the Satinsky clamp. This precluded the need for laparoscopic vascular suturing after tumor resection.

There are significant limitations to the use of this technique. It can only be used to treat renal masses with tumor thrombus that have minimal extension into the IVC. In other words, had the tumor thrombus been more extensive, it would not have been appropriate to significantly narrow the IVC using the stapler. Furthermore, it would not have been advantageous to have created a positive surgical margin using our described technique. Indeed, pathology confirmed negative surgical margins in our resection specimen. Nevertheless, we were prepared to use a Satinsky clamp to control the IVC and also fully prepared to open the patient if full vascular control of the IVC was required.

Our procedure was also complicated by the development of subclinical pulmonary emboli. The authors admit that it is possible that the pulmonary emboli may have propagated from the manipulation of the tumor thrombus. On the other hand, there is no evidence that open resection of the tumor would have prevented this complication.

CONCLUSIONS

We present a novel technique for laparoscopic resection of a renal mass with associated level II thrombus using a hand-assisted approach. By application of traction to the kidney after mobilization of the cava and use of an endoscopic vascular stapler, the mass was removed without the need for laparoscopic vascular sutures.

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CONFLICT OF INTEREST

None declared.

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Correspondence address:
Dr. Patrick P. Luke
Division of Urology
London Health Sciences Centre
339 Windermere Road
London, Ontario, N6A-5A5, Canada
Fax: + 5 19 663-3344
E-mail: patrick.luke@lhsc.on.ca

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Behavioral Alarm Treatment for Nocturnal Enuresis

Rodrigo F. Pereira, Edwiges F. M. Silvares, Paula F. Braga

Behavior Therapy Laboratory, Institute of Psychology, Universidade de Sao Paulo, Sao Paulo, SP, Brazil

ABSTRACT

Purposes: To investigate the efficacy of alarm treatment in a sample of Brazilian children and adolescents with nocturnal enuresis and relate treatment success to age and type of clinical support.
Materials and Methods: During 32 weeks, 84 children and adolescents received alarm treatment together with weekly psychological support sessions for individual families or groups of 5 to 10 families.
Results: 71% of the participants achieved success, defined as 14 consecutive dry nights. The result was similar for children and adolescents and for individual or group support. The time until success was shorter for participants missing fewer support sessions.
Conclusions: Alarm treatment was effective for the present sample, regardless of age or type of support. Missing a higher number of support sessions, which may reflect low motivation for treatment, increased the risk of failure.

Key words: *enuresis; behavior therapy; child; adolescent; group therapy*
Int Braz J Urol. 2010; 36: 332-8

INTRODUCTION

According to the International Children Continence Society, nocturnal enuresis is defined as discrete incontinence episodes while an individual is asleep (1). Children must be at least five years old to be diagnosed with enuresis. In addition to that, the DSM-IV criteria states that the involuntary voiding must occur at least twice a week for at least three months (2). Nocturnal enuresis is one of the most frequent problems of childhood, affecting up to 15% of children from 5 to 7 years of age and 1 to 2% of young adults (3-6). However, if DSM-IV criteria are employed, the prevalence of enuresis is around 2.6% (3). The variation in the criteria employed by different investigators to define enuresis makes it difficult to establish a precise prevalence rate (5).

The etiology and underlying physiological mechanisms of nocturnal enuresis are heterogeneous (7). Nevertheless, there is consensus concerning the notion that nocturnal enuresis arises from a combination of lack of vasopressin release during sleep or bladder hyperactivity and the inability to be aroused from sleep by bladder sensations (8). There clearly is a genetic basis at the origin of these phenomena (9), and the difficulty in waking up when the bladder is full is a sign of problems in the maturation of the central nervous system (10).

Both pharmacological and behavioral treatments are currently available for nocturnal enuresis. Desmopressin acetate, the most effective drug treatment, reduces the production of urine during the night, significantly decreasing wetting (11). The preferred behavioral treatment is alarm conditioning (12), associated with a success rate of 65% and 42% of relapse (13). Desmopressin acetate is no better than alarm or alarm plus desmopressin acetate in the long term (14).

Some factors may affect the response to alarm treatment, especially those of a psychological nature, such as marital conflict, lack of motivation and parental punishment (13). The physiological aspects associated with a poor response to alarm treatment include the difficulty to wake up with the sound of the device (15). The literature concerning the impact of enuresis severity on the outcome of alarm treatment is contradictory, with both positive (13) and negative (16) impacts being reported.

There is a dearth of studies on the prevalence and severity of enuresis in the Brazilian population. A study carried out with a probabilistic sample in an urban center in southern Brazil (17) has revealed a 20.1% prevalence of nocturnal enuresis in boys and 15.1% in girls based on the criterion of one wetting episode per night. This lack of studies may lead to a low level of information about enuresis and other lower urinary tract diseases among professionals that deal with children, such as caregivers and school teachers (18).

The main objective of the present study was to determine the success rate of alarm treatment in a population of Brazilian children and adolescents with nocturnal enuresis. We also aimed at identifying the relationship between age, type of psychological support and rate of success.

MATERIALS AND METHODS

The study sample included 84 children and adolescents from a university psychology clinic. Between 2002 and 2006, this group received care from four psychologists (graduate students at the university's Clinical Psychology graduate program). The participants were classified as children (6 to 10 years of age, n = 52) or adolescents (11 to 17 years of age, n = 32). Inclusion criteria were: age between 6 and 17 years, having wetting episodes at least twice a week for three consecutive months and absence of other disorders that could have caused the wetting episodes, such as diabetes or spina bifida. The sample included 19 adolescents that participated in the study conducted by Rocha, Costa and Silvares in the same research center (19).

All patients received full-spectrum home training (12), which consisted in the use of a bell-and-pad alarm during the night. Children and families were told to use the alarm daily in combination with cleanliness training and retention training as described by Houts (12). In addition, the families and patients were instructed to restrict fluid intake before going to bed, to keep regular sleep hours and to keep a record of night wetting episodes. Treatments lasted up to 32 weeks.

Each family participated in a weekly follow-up/support session lasting about one hour at the clinic. They were first screened for diagnosis and when there were about 20 families waiting for treatment, they were randomly assigned to participate in individual sessions (n = 51) or group sessions including five to ten families (n = 33). This procedure was undertaken about once or twice a year, and at each time a new randomization was made with the families previously screened. During the support sessions, the therapist reviewed the wetting record and made sure the procedures were being correctly followed. The children were accompanied by their parents or by caregivers in charge of monitoring the treatment at home.

Data were collected from the record filled out by the family, in which they informed whether the child was wet or dry on waking up. In the presence of bed wetting, the time when the alarm had rung and the approximate amount of urine, based on the size of wet patches (small, medium or large), were recorded. The treatment was considered to be successful if the child/adolescent remained dry for 14 consecutive nights during the treatment period. Treatment failure was defined as 13 or fewer consecutive dry nights or the family discontinuing the treatment (dropout). After success was achieved, a procedure (overlearning) to prevent relapse was performed. Overlearning involves drinking a small amount of water before going to sleep. The amount was determined according to the maximum voided volume expected for the child's age (age x 30 + 30 mL) and was increased every two consecutive dry nights, until the child was able to remain dry another 14 nights after reaching initial success. The alarm treatment was interrupted when overlearning was complete or when it was attempted two times unsuccessfully. In these cases, after the second attempt, more 14 dry nights were required for finishing the program.

Unpaired t-test was used to compare the frequency of enuresis episodes before treatment. Fisher's exact test was used to verify the relationship between success and the study variables (age and type of psychological support), and variance analysis was used to determine the time required to obtain success taking into consideration the study variables. ANOVA was used to analyze the variation in the time required to achieve success. Significance was established at $p < 0.05$.

RESULTS

To characterize the sample, the frequency of wetting episodes (severity of enuresis) in the sample was determined before the start of treatment. This information was not available for 10 participants, and thus 74 children and adolescents were considered (N = 74). Table-1 shows the distribution of the sample according to the frequency of night wetting episodes. Table-1 shows that more than half of the overall sample experienced bedwetting every night. This proportion was slightly larger in the group of adolescents, but the difference was not significant. Similarly, the mean number of weekly episodes for the overall sample (5.2) was similar to that for the two separate age groups.

The rate of severe enuresis in the sample is larger than that reported in prevalence studies (3). This is possibly due to the inclusion criteria used in this study and to the fact that the search for treatment may be more frequent when enuresis is more severe.

Table-2 shows the distribution of the two age groups and types of support in terms of treatment success and failure. Dropouts were included in the failure criteria.

Success was achieved in 71% of the sample. The success rate among children (6 to 10 years of age) and adolescents (11 to 17 years of age) was not statistically significant. Similarly, there was no statistical difference between the two types of support, although the failure rate was lower to participants receiving individual support (14% vs. 41% for group support) (Table-2). An analysis was also carried out to investigate if the onset of success differed in terms of age and session format. Figures 1 and 2 show the chance of obtaining success during treatment for these two variables.

Figure-1 shows that although success was achieved earlier in the group receiving individual support, the difference was not statistically significant. There was also no significant difference in time to achieve success according to age (Figure-2).

An analysis of time to achieve success related to session attendance is shown in Table-3.

The number of missed follow-up/support visits had a significant association with success: participants who missed less than 10% of sessions became dry faster than those who missed more than 10% of the sessions. It was also observed that the number of missed sessions was higher among those receiving group support: 62.5% of the participants missed more than 10% of the sessions vs. 37.5% of the participants receiving individual support ($p = 0.03$).

Table 1 – *Frequency of enuresis episodes before treatment.*

	Overall	**Children**	**Adolescents**	**p Value**
Mean number of wet nights per week (SD)	5.2 (2.02)	5.1 (2.05)	5.2 (2.01)	0.821
Frequency of Bed Wetting Episodes per Week - % (N)				
2 to 3	17.6 (13)	17.1 (7)	18.2 (6)	0.818
3 to 6	31.1 (23)	34.1 (14)	27.3 (9)	
More than 6	51.4 (38)	48.8 (20)	54.5 (18)	

Table 2 – *Success rate of an alarm technique with individual or group support in a sample of children and adolescents with nocturnal enuresis.*

	Success - N (%)	**Failure - N** (%)	**p Value**
	Overall		
	65 (71)	19 (29)	Not applicable
	Age		
Children	41 (79)	11 (21)	0.79
Adolescents	24 (75)	8 (25)	
	Type of Support		
Group	36 (59)	15 (41)	0.108
Individual	29 (86)	4 (14)	

COMMENTS

In the present study, the 71% success rate obtained by the participants is in accordance with previous results described in the literature - 65% on average (13). Considering more than half of our study participants had severe enuresis, the hypothesis that severity affects the results of treatment, either negatively or positively, may not be supported.

Age range has also been described as a predictor of failure, since adolescent enuresis is usually more difficult to treat (20). We did not observe a significant difference between children and adolescents, with both presenting similar success rates. However, with a broader sample, the slight difference in time to obtain success could appear as a significant factor.

The type of psychological support provided was not related to treatment success, as previously reported (13). Participants from families receiving individual support had similar success rates than those receiving group support; however, those receiving group support missed more sessions, an aspect associated with greater difficulty in achieving success. The percentage of group format participants that missed more than 20% of the sessions was 39.6%, against 17.5% of the participants of individual format. It is possible that the individual support leads to a greater commitment by the families, expressed in a better attendance to the sessions. Participants that missed more than 10% of the sessions, regardless of session format, took, on average, 5 more weeks to achieve success than those who missed less than 10% of the sessions. There seems to be a relationship between session attendance and success (13). The number of missed support sessions may be interpreted as a reflection of low adherence. It is likely that missing sessions in itself does not affect treatment, but rather, that it reflects a difficulty in following the prescribed steps, leading to a higher failure rate or to a longer interval until success achievement.

A limitation of this study was the absence of a control group and also of an analysis to determine the variability between therapists in terms of the support provided. In addition, a larger sample might

Table 3 – *Time, in weeks, to achieve success (defined as 14 consecutive dry nights) according session attendance.*

		Mean	**Standard Deviation**	**p Value**
Number of missed sessions	< 10%	7.3	5.17	0.007*
	> 10%	13.3	8.20	

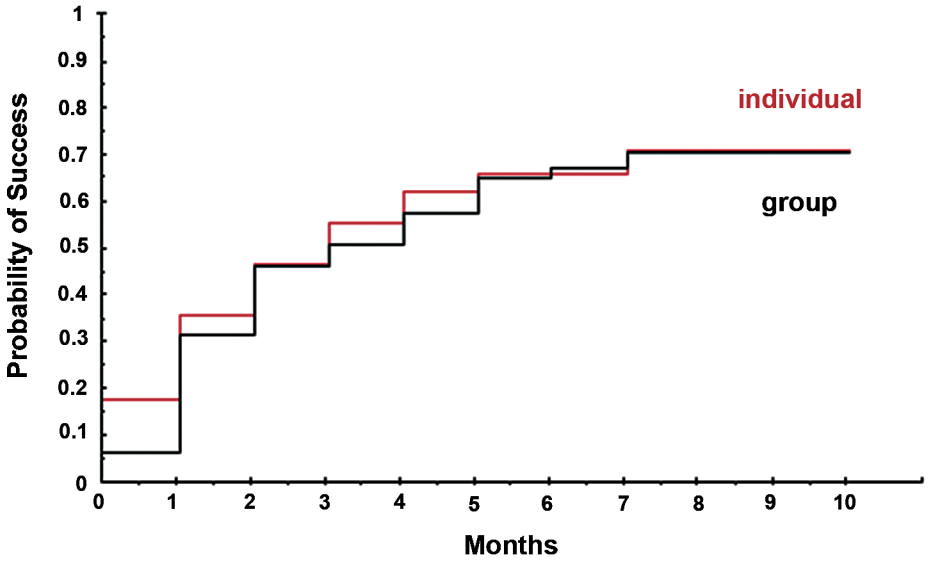

Figure 1 *– Probability of success according to session format.*

have been able to confirm the observed trend towards a better performance in participants receiving individual support, and to clarify the relationship between failure and missing support sessions. Therefore, it is not possible to determine which of these two juxtaposed variables determines treatment failure. A further limitation was the fact that treatment time was longer than that routinely practiced. This may

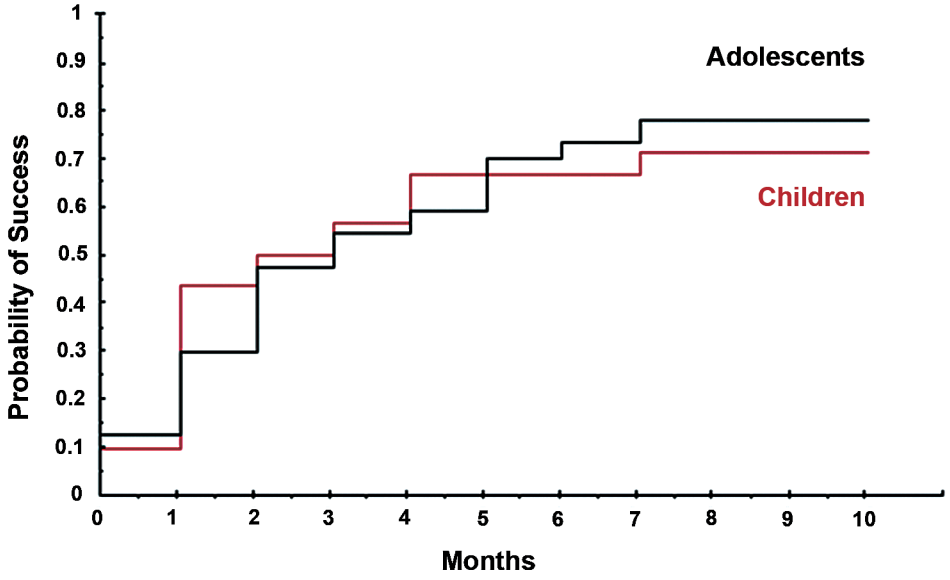

Figure 2 *– Probability of success according to age.*

have exaggerated the success rate, since the cases of success may have resulted from spontaneous remission of enuresis.

CONCLUSIONS

Treatment of nocturnal enuresis with an alarm technique was satisfactory in this Brazilian sample. The success rate was in accordance with that described in the literature. The results of treatment were similar for children and adolescents and for individual and group support. Failure to participate in support sessions was associated with a delay in success achievement. We believe that treatment with the alarm technique may be used in other Brazilian patient populations and that additional studies should be carried out to identify predictors of success and failure that are characteristic of this population.

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CONFLICT OF INTEREST

None declared.

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Correspondence address:
Dr. Rodrigo Fernando Pereira
Av. Prof. Mello Moraes, 1721 / Bloco F / Sala 30
Cidade Universitária
São Paulo, SP, 05508-030, Brazil
E-mail: rpereira@usp.br

EDITORIAL COMMENT

The authors should be congratulated for performing a study evaluating the results with alarm for enuresis in Brazilian children and adolescents. The authors' good results with this treatment demonstrate their high level of expertise in this field and that Brazilian patients can be successfully treated by this method. However, a significant drawback of the alarm treatment is the high dropout rate (reference 13 and 14 in the article). An intention to treat analyses is the most accurate way to evaluate the final success rate and it was not the case in this study. For instance, the alarm was indicated for 100 children and 30 discontinued the treatment (dropouts) even before patients could be entered into the study protocol. Suppose 45 (65%) out of those 70 had success with alarm. The rate of failure should be 55% (25 + 30 patients failed) not 35%. Unfortunately, the overall dropout rate was not stated. How many patients were not included in the protocol because they or the family was not adapted to the method? Since we do not have this information, the results of this study can be interpreted as overestimated. Also, the lack of a control group, the limited number of patients and the absence of clear randomization criteria does not permit to draw any conclusions regarding the value of a psychological support for these types of patients. It is interesting to note that children have the same success rate as the adolescents showing that this treatment is successful even in younger age.

Dr. Ubirajara Barroso Jr.
Rua Alameda dos Antúrios, 212 / 602
Salvador, BA, 40280-620, Brazil
E-mail: ubarroso@uol.com.br

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Comparative Study of Polypropylene and Aponeurotic Slings in the Treatment of Female Urinary Incontinence

Jorge A. Winckler, Jose G. L. Ramos, Bernadete M. Dalmolin, Diego C. Winckler, Marlene Doring

University of Passo Fundo, Rio Grande do Sul, and Federal University of Rio Grande do Sul, Rio Grande do Sul, Brazil

ABSTRACT

Purpose: Female stress urinary incontinence (SUI), the involuntary leakage of urine, is a highly prevalent social and hygiene problem, and various surgical techniques have been developed to correct it. This study used the technique of an aponeurosis sling made from the rectus abdominis muscle as a standard and compared the technique to a sling made with a polypropylene mesh, (Marlex®).

Materials and Methods: From 2000 to 2007, 158 women who underwent surgery for SUI with an aponeurosis sling, (average age 55 years), were used as a standard for comparison with 316 women who underwent surgery with a polypropylene sling (average age 55 years).

Results: The mean follow-up period was 3.65 and 3.56 years for the respective groups. The aponeurosis group showed a cure of SUI in 128 (81.0%), improvement in 23 (14.6%), and failure in 7 (4.4%). The polypropylene group showed a cure in 281 (88.9%), improvement in 23 (7.3%), and failure in 10 (3.2%) ($p = 0.083$). Urgency was observed in 19 (12%) of the aponeurosis group, and 28 (8.9%) in the polypropylene group ($p = 0.320$).

Conclusions: This study showed that the polypropylene mesh is an effective alternative to construct a sling for SUI in women. The results and rates of complication were comparable to the fascial sling from the rectus abdominis muscle aponeurosis.

Key words: *urinary incontinence; stress; suburethral slings; polypropylenes*
Int Braz J Urol. 2010; 36: 339-47

INTRODUCTION

Female stress urinary incontinence, classified as stress urinary incontinence (SUI) types I, II and III (1), is the objectively demonstrated involuntary leakage of urine. It is a social and hygiene problem, and results in high morbidity, social and sexual isolation, low self-esteem, and psychological trauma. It affects both job performance and home life (2) and is highly prevalent (3).

Historically, several surgical procedures have been developed for the treatment of female urinary incontinence: periurethral injection, transvaginal suspension, retropubic urethropexia, Burch's colposuspension, autologous fascial slings, laparoscopic colposuspension, AMS-800 artificial sphincter and procedures using pubovaginal belts and slings (4-10).

The objective of this study was to evaluate the use of a polypropylene mesh, (Marlex®), to construct a pubovaginal sling for use in surgery to correct SUI in women, assessing the results, rate of extrusion/infection of the mesh, compared with a fascial sling made from the rectus abdominis aponeurosis.

MATERIALS AND METHODS

In this surgical study for stress incontinence in women, we used the traditional technique of standard pubovaginal fascial sling and compared it with a sling that was made during the operation in which we use a segment of polypropylene mesh. The sling technique that was chosen for comparison in the study, always used a segment of polypropylene mesh (Marlex®) 10 x 1 cm with a pore size of 0.8 mm, which is placed in the middle urethra dissected previously with 2 polyglactin sutures 2-0 on each side of the screen, and passed along the endopelvic fascia on both sides of the urethra through the retropubic space close to the pubis, leaving a mini skin incision above the pubic region then tied one side to the other without tension (Figure-1).

To make the sling fascial sheath of the rectus abdominis muscle, we made a transverse incision above the pubic area 10 cm long to remove a fragment of the aponeurosis of the rectus sheath 10 cm long and one inch wide. The region above the symphysis was conventionally reconstituted. We used a 2-0 polyglactin suture on each side of the aponeurosis make the sling. On other occasions, a similar surgery is also performed using the initial surgery described above. The fascial sling is also placed in the middle urethra equal to that of polypropylene but not in the bladder neck as described in the original technique.

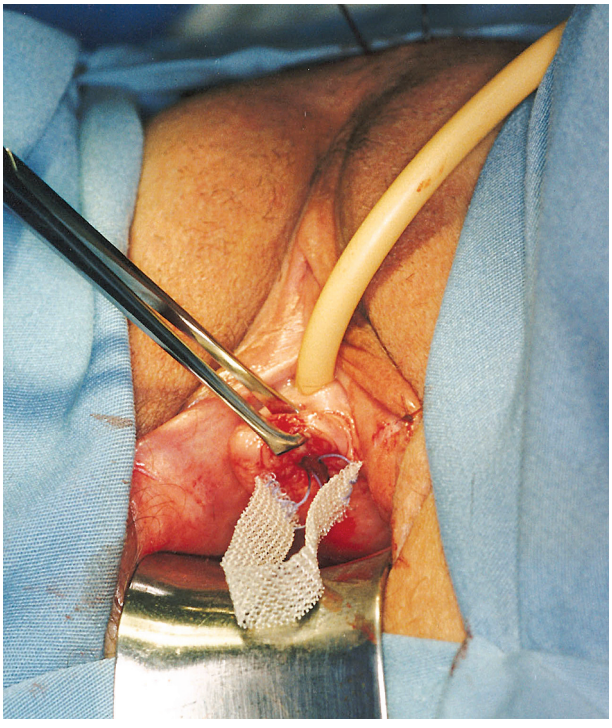

Figure 1 *– Polypropylene sling.*

This is a prospective non randomized study, with 959 women suffering from SUI, which took place from 2000 to 2007, in the city of Passo Fundo, Rio Grande do Sul, Brazil. The project was approved by the CEP/UPF/RS Research Committee under Protocol No. 129/2007. All the patients had their previous medical history recorded and a physical examination, a stress test with a full bladder, and an urodynamic study. The slings proposed were: a) an abdominal aponeurotic sling; and b) a polypropylene mesh sling (Marlex®). We informed patients as to the advantages and disadvantages between the two types of slings available and the patients were then free to choose which procedure they wished to receive.

The patients were divided into two groups: one in which a segment of aponeurosis of the rectus abdominis muscle (377 women) was used, and the other in which a segment of polypropylene mesh (Marlex®) (582 women) to construct the slings. After surgery, and the sample power calculation, 474 patients were selected to participate in the follow-up study, 158 in the aponeurosis group and 316 in the polypropylene group. After the criteria for inclusion or exclusion were established and certain patients had been excluded, the names of the patients were arranged alphabetically and in an ascending order until the calculated sample number was reached. If someone could not participate or could not be located, the next patient on the list was subsequently contacted.

Patients included in this study were between 35 and 70 years old at the time of the surgery, had stress urinary incontinence from intrinsic sphincter insufficiency or urethral hypermobility (pressure point leakage under stress below 60 cm H_2O in the first case and 60 to 120 cm H_2O in the second, according to McGuire et al. 1993) (11); or mixed urinary incontinence. Women with urogenital dystopia (cystocele larger than grade I, with prolapse of the uterus and/or vaginal vault), and those who had previously undergone surgical procedures for SUI, with failure or recurrence, were excluded.

The variables measured in the pre-operative medical workup were as follows: age, stated skin color, number of pregnancies/live births, types of births, weight, height, BMI, civil status, level of education, urgency prior to surgery, previous hysterectomy, rectocele, cystocele grade I, Valsalva leak point pressure, urodynamic study with leak point pressure under stress, and a score from 0 to 10 of satisfaction in relation to the bladder symptoms. The remaining variables: post-operative time in years, number of days hospitalized, number of days of vesical catheterization, whether or not there was extrusion/infection of the sling, resolution, frequency of urine leakage in the past 90 days, bladder urgency, score from 0 to 10 of satisfaction in relation to bladder symptoms, were answered in the questionnaire sent to the patients and revised with them during the re-evaluation consultation.

The patients were contacted by telephone about their willingness to participate in the study. The objectives of the study were explained to them, and they were invited to make an appointment for a consultation. The patients who accepted to participate received two questionnaires by mail, which they were requested to complete and sign; the questionnaire about the postoperative variables, and two copies of the free and informed consent form. During the consultations, the patients returned the documents signed, which were read with them, and in cases of questions about the study, the questionnaires were answered together, and they were given a physical examination and a stress test with full bladder. Those patients who were admitted underwent a cystoscopy to rule out erosion of the mesh into the urethral or bladder.

The results were classified according to Blaivas et al. (1991) (12), into three categories: cure - absence of incontinence; improvement - up to one episode of urine leakage in two weeks; and failure - more than one episode of incontinence per week.

As regards the data analyses the statistics program SPSS (v16) was used, initially to perform a descriptive analysis with the frequency distributions, means, and standard deviations. The Chi-square and Fisher's exact tests were used to assess the differences among the variables. The significance level was set at 5%.

RESULTS

Of the 474 women who underwent surgery for SUI with the sling technique, 158 received a segment of aponeurosis of the rectus abdominis muscle, and in 316, polypropylene mesh was used to construct the sling. The average age of the aponeurosis group was 55.20 years (range 37 to 69), and the polypropylene group had an average age of 55.69 years (range 36 to 69) ($p = 0.495$). In both groups, the predominant level of education was 4 to 11 years of schooling, the stated color was white, and the civil status was a stable relationship; most women had had two pregnancies and cesarian deliveries. The body measurements in the aponeurosis and polypropylene groups were, respectively: weight: 66.8 and 62.9 kg ($p < 0.05$); height: 1.65 m and 1.64 m ($p = 0.069$); and BMI: 24.6 and 23.4 ($p < 0.05$). In the urodynamic evaluation, detrusor hyperactivity was observed in 16 women (10%) of the aponeurosis group, and 27 (8.5%) of the polypropylene group (mixed urinary incontinence) ($p = 0.692$); leak point pressure under stress was between 60 and 120 cm H_2O in 116 women (73.5%) of the aponeurosis group, and 221 (70%) of the polypropylene group (urine loss due to urethral hypermobility) ($p = 0.518$); leak point pressure under stress below 60 cm H_2O in 26 women (16.5%) in the aponeurosis group, and 68 (21.5%) in the polypropylene group (urine loss from intrinsic sphincter insufficiency) ($p = 0.075$). Not only during the Valsalva leak point pressure test with a full bladder, but also during the urodynamic study, urine leakage was observed in 91.8% of the aponeurosis group and 92.1% of the polypropylene group ($p = 0.473$). In the remaining women, the diagnosis was confirmed by their previous medical history and by the pad test, and they were assigned to the urethral hypermobility group.

Regarding to the clinical aspects, the aponeurosis and polypropylene groups presented as follows, respectively: 52.5% and 60.4% reported 3 or more episodes of urine leakage per week ($p < 0.05$); 19% and 20.6% reported urination urgency ($p = 0.776$); 14.6% and 20.3% had had an hysterectomy ($p = 0.166$); 19.6% and 27.5% had had a perineoplasty ($p = 0.078$); 41.8% and 35.4% had rectocele ($p = 0.215$), and 55.7% and 57.6% had cystocele G1 ($p = 0.768$); concomitant perineoplasty was carried out in

Table 1 – *Characterization of the women who underwent surgery for urinary incontinence, according to a pre-operative urodynamic study and clinical history.*

Variables	Group				
	Aponeurosis		Polypropylene		
	N	%	N	%	p Value
Urethral hypermobility PPE: 60-120 cm H_2O	116	73.5	221	70.0	0.518
Intrinsic sphincteric deficiency PPE: < 60 cm H_2O	26	16.5	68	21.5	0.075
Detrusor hyperactivity	16	10	27	8.5	0.692
Frequency of urine leakage last 90 days pre-op					
Up to 1 time per week	-	-	1	0.3	0.000
Up to 2 times per week	32	20.2	14	4.4	
Up to 3 times per week	83	52.5	191	60.4	
Any movement, sneezing or coughing	35	22.2	62	19.6	
Even lying down, constant	8	5.1	48	15.2	
Urine leakage in pre-op urge stress test					
Yes	157	99.4	311	98.4	0.859
No	1	0.6	5	1.6	
Pre-operative urgency					
Yes	30	19.0	65	20.6	0.776
No	128	81.0	251	79.4	
Hysterectomy					
Yes	23	14.6	64	20.3	0.166
No	135	85.4	252	79.7	
Pre-op perineoplasty					
Yes	31	19.6	87	27.5	0.078
No	127	80.4	229	72.5	
Pre-op rectocele					
Yes	66	41.8	112	35.4	0.215
No	92	58.2	204	64.0	

67 (42.4%) and 109 (34.5%) (p = 0.114) (Table-1). The mean number of hospitalization days was 3 and 1.1 days ($p < 0.05$), and for vesical catheterization was 0.4 and 0.1 days ($p < 0.05$), for the aponeurosis and polypropylene groups respectively, i.e., was significantly smaller for the polypropylene group. There were no cases of intestinal or vascular perforations or hematomas in either group. There was perforation of bladder with needle in 5 cases in the aponeurosis group, and in 12 cases in the polypropylene group: in all these cases, hematuria was observed in the Foley catheter and urine collector soon after the passage of the needle. This was removed and reinserted closer to the pubis, and the Foley catheter left indwelling for three days, with no consequences in any of the cases (p = 0.72). In all the cases of both groups, a transoperative cystoscopy was performed, and no other injury was observed.

The aponeurosis group had a mean follow-up time of 3.65 years (range 1 to 7 years), and the polypropylene group had a mean follow-up time of 3.56 years (range 1 to 7 years). In the aponeurosis group, 128 cases (81.0%) resulted in a cure of SUI, improvement occurred in 23 (14.6%), and failure in 7 (4.4%). The polypropylene group showed a cure in 281 cases (88.9%), improvement in 23 (7.3%), and failure in 12 (3.8%). The rates of cure, improvement, and failure did not differ significantly between the groups (p = 0.083) (Table-2). In the stress test with full bladder (Valsalva), 91% of the aponeurosis group and 92% of the polypropylene group showed no urine leakage (p = 0.859). The patients who presented a single improvement in both groups were referred for pelvic physiotherapy with poor adhesion. Urinary urgency was observed in 19 (12%) of the aponeurosis group and 28 (8.9%) of the polypropylene group (p = 0.320) and were treated with anticholinergic therapy.

We classified extrusion and/or infection of the sling together, because there was vaginal secretion in both cases. In the aponeurosis group, 7 (4.4%) had a vaginal extrusion/infection, and of the polypropylene group, 15 (4.7%) had this condition (p = 0.877) (Table-2). In the cases of vaginal extrusion/infection in the aponeurosis group, 2 (28.6%) resolved spontaneously and 5 (71.4%) required surgical removal. As regards the cases of vaginal extrusion/infection in the polypropylene group, 5 (31.2%) resolved spontaneously and 11 (68.8%) required surgical removal (p = 0.899) (Table-2). The patients with extrusion / sling infection received fibrinolysin 3 times a day for two weeks. Those who did not improve underwent surgery with removal of infected or exposed sling but later started to have leaking urine. After 6 months, some patients underwent surgery again with the polypropylene sling. After the second surgery, the majority of them had some degree of temporary urgency.

Six women (3.8%) in the aponeurosis group and 7 (2.2%) in the polypropylene group (p = 0.374) underwent urethrolysis within 60 days, due to urine retention (Table-2). All patients had improvement in urinary flow and bladder emptying, but also showed some degree of urgency. In our experience, the patients who required surgery again complained of some urinary urgency, had a low adherence to anticholinergic medication but improved after 90 to 180 days with pelvic floor exercises or because of the body adjustment over time.

A cystoscopy was performed after more than one year after the surgery, in 66 (41%) patients in the

Table 2 – *Number and frequency of urine leakage, vaginal extrusion/infection with resolution and retention/urethrolysis in women who underwent the surgical sling technique for SUI with aponeurosis or polypropylene.*

Variables	Group				
	Aponeurosis		Polypropylene		
	N (158)	%	N (316)	%	p Value
Urine leakage last 90 days (post op)					
Never	128	81.0	281	88.9	0.083
Up to once in two weeks	23	14.6	23	7.3	
More than once a week	7	4.4	12	3.8	
Vaginal extrusion/infection					
Yes	7	4.4	15	4.7	0.877
No	151	95.6	301	95.3	
Resolution extrusion/infection					
Spontaneous	2	28.6	5	31.2	0.899
Surgical removal of the sling	5	71.4	10	68.8	
Retention urethrolysis after 60 days					
Yes	6	3.8	7	2.2	0.374
No	152	96.2	309	97.8	

Table 3 *– The mean of the scores from 0 to 10, given by the patients prior and after the procedure with aponeurosis or polypropylene sling.*

Variable	Group	N	Mean	SD	p Value
Score 0-10 (satisfaction prior procedure)	Aponeurosis	158	2.2	1.4	0.000
	Polypropylene	316	2.1	1.3	
Score 0-10 (satisfaction after procedure)	Aponeurosis	158	9.4	1.2	0.000
	Polypropylene	316	9.6	1.0	

aponeurosis group and 146 (46.2%) in the polypropylene group. There were no cases of sling erosion to the bladder or urethra in both groups (p = 0.414).

The average scores from 0 to 10 given by the patients after the surgery (9.4) and (9.6), respectively to aponeurosis and polypropylene, showed a great improvement in both groups over the mean scores (2.2) and (2.1) that they gave prior to surgery. Student's-t-test for paired samples indicated a significant difference between the mean pre- and post-operative scores in the aponeurosis group (p = 0.000), and also in the polypropylene group (p = 0.000) (Table-3).

COMMENTS

The objective of surgical treatment for SUI in women is to re-establish urethral resistance, in order to prevent urine leakage during an increase in abdominal pressure, preserving adequate bladder filling for voluntary and spontaneous urination.

Studies comparing commercially available synthetic slings with the pubovaginal fascial sling or Burch's colposuspension (13-17) have shown that these slings are promising, but there is still the question of cost, which is prohibitive in our situation. The option of an aponeurotic sling either from the rectus abdominis or a polypropylene mesh for the surgeon to use to construct the sling appears to be an accessible procedure, and the cost is compatible with the conditions in our clinical working environment.

After several years using both the aponeurosis made from the rectus abdominis and the polypropylene sling, we have established two cohorts of patients whom are currently being monitored. Upon comparing both products and data reported in the literature, it appears that the polypropylene sling is a viable procedure and that it can be used with results and rates of complications comparable to the aponeurosis, if the procedure is carried out with technical rigor, rapid surgery, minimal exposure of the surgical field, a small incision, good tissue padding, etc.

In our study, we observed extrusion or infection of the sling in 4.7% of the polypropylene group and 4.4% of the aponeurosis group. In a doctoral thesis, de Almeida et al. (18) described an experiment in rats using slings composed of autologous fascia, pig intestine submucosa, tension-free vaginal tape (TVT) and Marlex®. These authors concluded that the material that caused the least inflammatory reaction and produced the least collagen was the autologous fascia. The TVT and the Marlex® produced similar reactions.

Furthermore, in our study, with an average follow-up time of 3.56 and 3.65 years for the polypropylene and aponeurosis groups, the mean of the scores from 0 to 10 given by the patients after the procedure indicated high satisfaction in relation to the mean score that they assigned prior to the procedure, with both techniques (p = 0.000). Haab et al. (19), with 4 years of follow-up of a pubovaginal sling for the treatment of SUI for intrinsic sphincter insufficiency and using an self-assessed questionnaire, confirmed the high satisfaction rate of the patients, in spite of their symptoms of urinary urgency. Rodrigues et al. (20), using polypropylene mesh for the construction of sling for SUI, concluded that the complications and cure rates can be compared with TVT, and should be

considered an alternative for patients with SUI. Amaro et al. (21), with a prospective randomized study of quality of life after autologous fascial sling and TVT for SUI, had similar results between the AFS and TVT, except that the operative time was shorter in the TVT.

In our 16 cases of vaginal extrusion/infection in the polypropylene group, 5 (31.2%) spontaneously resolved, and 11 (68.8%) required surgical removal of the sling. In the 7 cases of vaginal extrusion / infection of the aponeurosis group, 2 (28.6%) spontaneously resolved and 5 (71.4%) required surgical removal. Woodruff et al. (22) carried out a comparative histological study of sling materials in women who underwent the repair, in which a portion of the sling was removed in order to analyze the inflammatory response, encapsulation, neovascularization, and fibroblastic infiltration. The tissues analyzed were polypropylene, aponeurosis (autologous fascia), pig fascia, and fascia from cadavers. There was no degradation of the polypropylene insert, and the degree of fibroblastic infiltration was better. Also greater neovascularization was found in the polypropylene and aponeurotic slings. There was no encapsulation of the polypropylene or the aponeurosis. Giant cells were found in the pig fascia, and these were encapsulated to the highest degree. There was greater degradation of the cadaver fascia. Almeida et al. (23) describe a modification of the cadaveric prolapse repair and sling using cadaveric fascia lata fixed over rectus abdominis muscle. After an average of 6 months they observed 65% cure rate of incontinence and 12% improvement of incontinence but did not report any degradation of the fascia.

Cystoscopy was performed during surgery in all patients and bladder perforation was observed in 0.36%. Although hematuria was present in the Foley catheter, suggesting drilling, we concluded that cystoscopy is necessary when a retropubic sling is used, unlike Fischer et al. (24), who concluded that a transobturator sling is as effective as the retropubic sling, and does not require cystoscopy.

In our study, patients resulted in failure, 7 aponeurotic group, and 12 in the polypropylene group needed surgery again. We repeated the procedure with a polypropylene sling (Marlex ®), avoiding any local manipulation and found a satisfactory improvement. We avoided dissecting the tape adhered to the periurethral tissues, as proposed by Eandi et al. (25), who used TVT for the correction of SUI in women who had undergone a synthetic sling, with failure of the procedure.

CONCLUSIONS

The use of a segment of polypropylene mesh (Marlex ®) for the construction of a sling for urinary incontinence in women is safe and effective in improving and cure of patients. It is easy to perform, inexpensive, showed low failure rates and low rates of extrusion / infection in this study, however, further studies with other materials will be required to select the ideal sling.

CONFLICT OF INTEREST

None declared.

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Correspondence adrress:
Dr. Jorge Antonio Winckler
Rua Uruguai 1992/202
Passo Fundo, RS, 99010-112, Brazil
E-mail: jorgewinckler@uol.com.br

EDITORIAL COMMENT

The authors review a large number of female patients who were treated for stress urinary incontinence with either a pubovaginal sling using autologous fascia or one made of polypropylene mesh. The authors fashioned their own sling and did not use an industry manufactured kit. Their follow-up was over 3 years and the patient population included no truly elderly patients, with the oldest patient being 70 years of age. The patients were randomized by personal choice after a review of options available. Findings included that the days of hospitalization were markedly less (3 vs. 1.1) for the mesh sling versus the autologous fascial sling and that the rates of vaginal extrusion and infection were similar to both populations. In addition, the number of patients who required urethrolysis secondary to obstructive voiding dysfunction was markedly similar.

The authors should be commended on publishing the results on a large population of patients and the results of their experience. That these surgeons were able to reach a level of success that compared to the gold standard pubovaginal sling with autologous fascia using a self-made mesh sling makes a strong statement regarding the need for industrial supplied kits. This finding has been noted by other thought leaders and warrants contemplation by the reader (1).

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Dr. Steven P. Petrou
Professor of Urology, Associate Dean
Mayo School of Graduate Medical Education
Jacksonville, Florida, USA
E-mail: petrou.steven@mayo.edu

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Tumor Banks: The Cornerstone of Basic Research in Urology

Sabrina T. Reis, Emanoela B. Feitosa, Jose Pontes-Junior, Camila C. Marin, Daniel K. Abe, Alexandre Crippa, Alberto A. Antunes, Adriano J. Nesrallah, Luiz C. Oliveira, Leopoldo A. Ribeiro-Filho, Miguel Srougi, Katia R. M. Leite, Marcos F. Dall'Oglio

Laboratory of Medical Investigation (STR, JPJ, KRML), Division Urology (EBF, JPJ, CCM, DKA, AC, AAA, AJN, LCO, LARF, MS, MFDO), School of Medicine, University of Sao Paulo, Sao Paulo, Brazil

ABSTRACT

Purpose: Tumor banks have the primary responsibility for collecting, cataloging, storing and disseminating samples of tissues, cells and fluids, which are used by researchers to identify diagnostic molecular markers, prognostic indicators and therapeutic targets. The objective of this review was to describe a simple, reliable and reproducible protocol for obtaining and storing samples of urological tumors.
Materials and Methods: Urogenital tumor tissues were collected by the surgeons from the Urology Division of University of Sao Paulo Medical School. The obtained surgical specimens were immediately placed in liquid nitrogen, dry ice or in a tube containing RNAlater ®, and then stored by cryopreservation (-80°C). A mirror fragment was fixed in 10% formalin processed routinely and embedded in Paraplast®.
Results: We developed a protocol for the collection, cataloging, storage, conservation and use of tumor samples. During a period of one year the Urological Tumor Bank of the Urology Division stored 274 samples of prostate, bladder, kidney, penis and testicle tumors of different histological types, 74 urine and 271 serum samples.
Conclusions: Having biological materials characterized and available along with the clinical patient information provides an integrated portrait of the patients and their diseases facilitating advances in molecular biology. It also promotes the development of translational research improving methods of diagnosis and cancer treatment.

Key words: *biological specimen banks; urogenital neoplasms; tissue banks; pathology; molecular biology*
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INTRODUCTION

According to the Council of Europe, (1997), in Commentary 137 to article 22, "a tumor bank is an organization responsible for collecting, cataloging, storing and disseminating samples of tissues, cells and fluids for the investigation of diagnostic molecular markers, definition of prognosis and identification of therapeutic targets (1), for facilitating the discovery of new therapies and new drugs, and for other applications yet to be discovered" (2).

All organs of the urogenital tract are potential targets of malignant tumors, and although prostate cancer has the higher incidence, there is a need for the study of tumors of the bladder, kidney, urethra, testicles and penis to help optimize methods to be applied in diagnosis, prognosis and treatment of these diseases. The tumor bank of the Urology Division at

the University of Sao Paulo Medical School (USPMS) was established in 2008 and differs from the other banks by storing only samples of urological tumors, in order to increase the number of basic studies and clinical research.

Brazil has three major banks that store tumor specimens of various types of cancer: the Barretos Cancer Hospital has 19,000 samples, AC Camargo Cancer Hospital has 13,000 samples and the National Cancer Institute has 7,000 samples.

The objective of this review was to describe a simple, reliable and reproducible protocol for obtaining and storing samples of urological tumors; to clarify basic concepts related to tumor banks, their organization, relevance, quality and ethics; and to describe the tumors in the bank created by the Urology Division of USPMS.

Two principles are fundamental for good basic and clinical research: the accuracy of clinical information and outcome of patients treated by cancer and the quality of tumor samples that will allow the search for molecular abnormalities involved with neoplastic development and progression. A tumor bank with an effective protocol allows researchers to store and access tumor tissue samples under ideal conditions for research and recovery of patient data (3). This systematic organization of information allows the development of cancer research with solid scientific conclusions (4).

According to Teodorovic et al. (5) tumor banks contribute to translational research by promoting more and better integration between clinicians and researchers. Translational research is an integration of clinical and laboratory research aiming the improvement of prevention, diagnosis and treatment of diseases via the practical application of scientific discoveries (5-7). The identification of a tumor or a biological marker allows a better understanding of the pathology, diagnosis, prognostic indicators, most appropriate therapy and the potential of recurrence. For example, prostate-specific antigen serves as a marker for prostatic cancer (5) and is used by urologists to better assess patients and to obtain greater precision in evaluating the diverse characteristics of the disease.

According to Alimena et al. (4), the idea of using a therapy that reaches only the neoplastic cells and the identification of markers capable of distinguishing sensitive patients from patients resistant to first-line therapy are both the result of the creation of tissue banks.

Pathologists and molecular biologists have been responsible for such studies, conducting laboratory research with the practical goal of not only contributing to clinical knowledge, but also guiding the clinician in the evaluation of patients (4). Chu et al. (8) described molecular biology as a discipline that uses the techniques available to study diseases and their implications.

The tumor bank of the Urology Division of USPMS was created with the goal of aiding a new line of research in urological oncology. Having these biological materials available and characterized, along with the clinical information of the patients, provides an integrated portrait of the patients and their illnesses, enabling advances in molecular biology. Tumor banks may be useful in the future because constant medical and technological advances in early diagnosis and pre-operative therapies will reduce the number of surgeries for tumor removal, thus jeopardizing the collection of tumor tissues. Therefore, a network of tumor banks must be organized to ensure appropriate and responsible use of the materials (9).

Informatics (10) can facilitate patient registration, specimen tracking, tissue cataloguing, quality assurance, and specimen availability. The ability of databases to organize and present desired information can also aid in tracking informed consent and institutional compliance and be could used to generate tissue bank inventory reports to match investigator requests with specimen availability.

The components of a system must be faultless in order to allow efficient data entry, queries and report preparation, and must also allow rapid deployment of new services. The Urology Division of USPMS has a computer software exclusively established for the function of its tumor bank and also an electronic file system that allows the professionals involved in research to gain access to all clinical and laboratory information from each patient.

Each country defines the rules it believes are necessary to protect its citizens. Few countries, including Iceland and Sweden, have a law specifically related to tumor banks. The majority have Research Ethics

Table 1 *– Procedure for storage of collected tissue.*

Cryopreservation (- 80°C)	**Embedding in Paraplast®**
Benefits	Benefits
Morphological studies of high quality	Cheaper
Molecular, immunohistochemical and cytogenetic analyses	Half-life unlimited
Extraction of high quality DNA, RNA and protein	Histological morphology of high quality
Disadvantages	Disadvantages
Half-life: 1 decade or more	The genetic material may be damaged
More expensive and more difficult	

Committees (REC) that has to approve research that will use the samples of tumor banks, acting only once the tissue is stored but not for storage of samples.

Oosterhuis et al. (2) summarized the principles to which all tumor banks must comply: i) Protect the interests of donors; ii) Give patients full information about the project and appropriate research; iii) Uphold and ensure the balance between the interests of science and donors; iv) Prohibit the commercial use of human tissue.

In Brazil, the ethical issues related to research activities involving human beings are governed by the Guidelines and Standards for Research in Human Beings, introduced by Resolution 196/96 of the National Health Council (11). Resolution 347/05 regulates the storage and use of human biological material for research purposes (12).

According to Resolution 196/96, the respect due to human dignity requires that all research is conducted after free and informed consent of patients. The patient must sign a form to agree that their material can be included in the tumor bank, and when that material is part of a study approved by the tumor bank and the REC, the patient must be contacted and has to sign an additional form referring to the study that seeks the material. In cases where it is impossible to obtain the consent of the patient (e.g. death,), this fact must be documented with an explanation of the cause of failure and the opinion of the REC.

Resolution 347 states that the REC should be informed of the formation of a tumor bank and of its objectives and responsibilities.

MATERIALS AND METHODS

Standard Operational Procedure of the Urological Tumor Bank

Biological materials are stored by cryopreservation (-80°C) and in paraffin blocks (Table-1). After surgical specimens are removed, the fresh tissue is immediately placed in liquid nitrogen, dry ice or in a tube containing RNAlater ® (a solution that preserves the genetic material of the tissue for a longer period), which is then stored at -80°C. The freezer is localized in a special room designed for -80ºC freezers where freezer temperature is controlled 24 h by a computerized system MV2000 (Yokogawa). Additionally a generator is installed to supply the equipment in case of energy failure. The material is available only to accredited researchers in the Urology Division and is used after approval of the REC. A mirror fragment of the specimen frozen is fixed in 10% buffered formalin routinely processed and embedded in Paraplast®. Central morphologic reviews are performed on the formalin-fixed samples, including assessment of tumor diagnosis, percent of tumor, stroma, and necrosis.

The physician responsible for the surgery is also responsible for the collection of the Consent Form and the tumor sample. Immediately after surgical removal, a fragment of the tumor is removed and put into a plastic tube resistant to low temperatures with RNAlater ® and is immediately labeled with a code for identification.

At the tumor bank of the Escola Paulista de Medicina / UNIFESP (4), as well as in our bank, the procedure is performed in the operating room with the patient anesthetized or under regional blockade. The collection neoplastic tissue samples are performed with a scalpel in the areas affected by the tumor. A preliminary assessment of the material is performed by direct palpation in areas more representative of the tumor. Then fragments are removed to provide material for pathological and genetic studies. The minimum size accepted for samples to be stored in a bank is 0.5 x 0.5 x 0.3 cm. Completion of the identification data for the donor and the identification data for the sample of tissue is the sole responsibility of the technical team.

An important issue related to the collection of surgical specimens for tumor banking in urology is the histological verification process. This is necessary due the potential risk that no tumor is present in the collected fragments. It can occur in cases where the tumor volume is small or not able to be seen as in prostate cancer specimens. Therefore, before banking, the obtained tissue needs to be histologically verified to ascertain the presence of neoplasic cells. The mirror fragment fixed in formalin and embedded in Paraplast® is the better solution for this problem. But in cases where this procedure has not been done, before the experiments using the samples, a slide should be cut in a cryostat and stained in hematoxylin and eosin to verify the presence and amount of tumor represented in that specific tissue fragment.

Another important aspect is the precise site of fragment collection, especially for large tumors. A 10 cm kidney cancer may show histological and molecular heterogeneity when different parts of the tumor are examined. In bladder tumors, although the large amount of exophytic tumor appears homogeneous macroscopically, the bladder tumor base may be different at the molecular level. For this reason, our collecting protocol mandates that at least two different areas should be sampled for each case.

A nurse is responsible for collecting blood and urine, for labeling the samples and placing them in cold storage. A biologist is responsible for collecting all the material, processing the samples, cataloging them and storing them in a freezer at -80°C.

If there is any problem with the tube used to store the tissue, it must be discarded and replaced. The samples should not remain more than 30 minutes without optimal storage conditions to prevent degradation of genetic material (DNA, RNA and proteins).

Another aspect that deserves mention is biosafety. Sastre-Garau (13) advised that the team involved must treat all materials as if they were contaminated, as there are risks inherent in handling biological samples, which could be infected by pathogens such as virus from human immunodeficiency and hepatitis B and C.

Infrastructure

There are minimum requirements for the operation of a tumor bank. A liquid nitrogen container or a -80°C freezer is required for sample storage, and thus physical space for these systems is necessary. Space is also required for processing the samples, the freezing unit, RNAlater ® later, media storage (boxes and tubes), computer equipment (computer and printer) and the team (physicians' surgeons, pathologists and nurse biologist). A continuous accounting system is essential in tumor banking to control the withdrawals and inclusion of samples at any time.

Auditing

An external audit is also necessary to ensure adequacy and quality control for any tumor bank. We acknowledge that the tumor bank must have a large numbers of samples sufficient for the completion and validation of any type of protocol but the most important aspect is the quality of the stored material, verified and complemented by ongoing clinical data accrual instead of sample size.

The establishment of a tumor bank in large hospitals has some advantages as a large and diverse population which is available at our Institution. Our tumor bank has been in existence for approximately one year and already has large numbers of samples that have been used in various studies involving urological neoplasms.

Table 2 *– All material collected from the tumor bank of the Division of Clinical Urology, Oncology sector from August 2008 to June 2009.*

Anatomical Location of the Tumor	Quantity
Tumor samples	
Prostate	130
Bladder	83
Kidney	51
Penis	03
Testicle	07
Total	274
Serum	271
Urine	74

RESULTS

From August 2008 to June 2009 we collected 274 samples from different urogenital tumors as described in Table-2. There are also 74 urine and 271 serum samples that have been collected just before surgical procedure.

COMMENTS

Understanding cancer at the molecular level is a very important step for the identification of new markers for diagnosis and prognosis of cancer, representing a chance to create opportunities to develop target therapy. For this reason, it is of great importance to build a tumor collection in good storage conditions (2).

Urological tumors are a serious clinical problem, as they include high prevalence neoplasms such as prostate cancer and aggressive tumors such as kidney and bladder carcinomas. With the development of molecular biological techniques, the use of human neoplastic tissue is of great importance for cancer research. Therefore, we were prompted to begin development of protocols with extensive clinical and surgical data in order to create a tumor bank.

Regarding the storage of tumors, there are advantages and disadvantages to storing samples in a -80°C freezer and freezing in liquid nitrogen. The benefits of the freezer are the ability to store about 15,000 2 mL Eppendorf tubes, with easy access and less infrastructure requirement. The disadvantages are the high cost, the fragility of the equipment and its dependence on energy (4). To solve this problem there are liquid nitrogen backups that keeps the freezer at low temperature when lack of energy occurs, however only for a short period of time.

Storage in liquid nitrogen renders the access of the specimens difficult and requires constant maintenance of the level of nitrogen. The advantages are preservation at -170ºC and independence from energy (13). We chose to store the tumor bank in a -80°C freezer. It is important to mention that freezers must be routinely checked to guarantee the constant temperature, crucial for the maintenance of integrity of surgical specimens, urine and serum. Also, a back-up of gas supply or generator is imperative in case of electric energy failure. In our case we have a room in the main building of University of Sao Paulo Medical School specially designed for -80ºC freezers containing a computerized system for temperature control and generators.

It is imperative to record basic information from patients and their diseases to make a tumor bank useful for science. Gender, age, clinical and histopathological diagnoses, TNM classification, specification about a tumor as primary, metastatic or recurrent, occurrence of a previous treatment, type of sample, and most importantly the outcome of the patients should be recorded and be easily retrieved when necessary (14).

Finally, we must make clear that the benefits offered by research with human tumor or normal tissue from donors do not negate the serious and complex issues of medical-legal ethics. All information provided must be maintained in a way that guarantees donor anonymity. We also emphasize that the main goal of research must first be to afford some benefit to the patient and not to the researcher (8).

CONCLUSION

A tumor bank can be an instrument of great help for scientific research, as it offers tumor samples to researchers that have been stored under optimum

conditions of preservation. Through analysis of these samples, the researcher can better understand the cancer regarding the diagnosis, prognosis, prophylaxis and treatment. A well-organized and structured tumor bank facilitates and enables basic research discoveries that can improve population health.

The disclosure of the protocol used by the urological tumor bank of the Urology Division of USPMS should assist other centers in training. Standardization of the handling of the specimens, collection and storage and having a link between tumor banks will also increase the quantity and scope of research through the exchange of samples. In addition, by comparing information from databases at different locations, the regional characteristics of tumors can be studied and related to the habits of the respective populations.

CONFLICT OF INTEREST

None declared.

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Correspondence address:
Dr. Marcos Francisco Dall'Oglio
Fundação Faculdade de Medicina
Av. Dr. Arnaldo 455, 2º andar, sala 2141
São Paulo, SP, 01246-903, Brazil
E-mail: sasareis@gmail.com

EDITORIAL COMMENT

That paper of Reis and co-workers is of great importance in the field of research since that will allow studies on a very well organized source of human materials kept in very good conditions. It is very important to save a lot of tissues (together with blood) and for many years. Thus, in order to avoid any problems and to meet scientists requirements for research project it is necessary to save duplicates / triplicates of tissues in at least two different places (not necessary in the same city). It is well known that saving tissues in only one -80°C freeze is dangerous and it is better to have different banks in order to avoid any problems of safety (in case of electric power defect) and security. I would suggest also to have a website in order to inform people in your country about the relevance of that bank and thus organize meeting for future scientific projects in that area. What is also important to consider is the cost of keeping these samples for many years with highly specialized apparatus as well as technicians who must be aware of these conditions.

Dr. Serge Carreau
Full-Professor
University of Caen Basse-Normandie
Biochemistry-IBFA
Caen, France
E-mail: serge.carreau@unicaen.fr

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UROLOGICAL SURVEY

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

Athanase Billis
State University of Campinas
Campinas, SP, Brazil

Andreas Böhle
Helios Agnes Karll Hospital
Bad Schwartau, Germany

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

Sean P. Elliott
University of Minnesota
Minneapolis, MN, USA

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

Manoj Monga
University of Minnesota
Edina, MN, USA

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

Adilson Prando
Vera Cruz Hospital
Campinas, SP, Brazil

M. Chad Wallis
University of Utah
Salt Lake City, Utah, USA

STONE DISEASE

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Chronic kidney disease affects the stone-free rate after extracorporeal shock wave lithotripsy for proximal ureteric stones

Hung SF, Chung SD, Wang SM, Yu HJ, Huang HS
Department of Urology, National Taiwan University Hospital and College of Medicine, National Taiwan University,Taipei, Taiwan
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Objective: To investigate the effect of renal function on the stone-free rate (SFR) of proximal ureteric stones (PUS) after extracorporeal shock wave lithotripsy (ESWL), as urinary obstruction caused by PUS can impair renal function, and elevated serum creatinine levels are associated with decreased ureteric stone passage.
Patients And Methods: From January 2005 to December 2007, 1534 patients had ESWL for urolithiasis, 319 having ESWL in situ for PUS; they were reviewed retrospectively. Patients requiring simultaneous treatment of kidney stones, placement of a double pigtail stent, or percutaneous pigtail nephrostomy tube were excluded. We divided patients into groups by chronic kidney disease (CKD) stage according to the estimated glomerular filtration rate (eGFR) of >/=60 and <60 mL/min/1.73 m(2). Stone-free status was defined as no visible stone fragments on a plain abdominal film at 3 months after ESWL. A logistic regression model was used to evaluate the possible significant factors that influenced the SFR of PUS after ESWL, and to develop a prediction model.
Results: The overall SFR of PUS (276/319 patients) was 86.5%; the SFR was 93% in patients with an eGFR of >/=60 and 50% in those with an eGFR of <60 (P < 0.001). After univariate and multivariate analysis, the three significant factors affecting SFR were an eGFR of >/=60, stone width, and gender, with odds ratios (95% confidence intervals) of 19.54 (8.25-46.30) (P < 0.001), 0.67 (0.55-0.82) (P < 0.001) and 0.16 (0.05-0.50 (P = 0.002), respectively. A logistic regression model was developed to estimate the probability of SFR after ESWL, the equation being 1/(1 + exp [-(3.8137 - 0.3967 x (stone width) + 2.9724 x eGFR - 1.8120 x Male)]), where stone width is the observed value (mm), eGFR = 1 for eGFR >/=60 and 0 for <60, and male = 1 for male, 0 for female.
Conclusions: Gender, eGFR >/=60 and a stone width of >7 mm were significant predictors affecting the SFR after one session of ESWL for PUS.

Editorial Comment

The authors do not state at what time point was the serum creatinine obtained that was utilized to calculate the estimated GFR. This is a critical omission. Ideally the serum Cr and GFR would have been evaluated after resolution of the obstructing calculus. This would identify those with true chronic kidney disease. In contrast, if these values were evaluated at the time of obstruction; the abnormality may have been post-renal. Indeed, if they have selected those patients with renal insufficiency due to severe obstruction, one would anticipate that these may be patients with more severe hydronephrosis or longer duration since onset of pain and obstruction; both of which could be independent predictors of failure of SWL. The observation that stone width is more critical than stone length in determining shockwave success may be important to consider when counseling patients.

Dr. Manoj Monga
Department of Urology
Cleveland Clinic Foundation
Cleveland, Ohio, USA
E-mail: endourol@yahoo.com

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Novel in vitro model for studying ureteric stent-induced cell injury

Elwood CN, Lange D, Nadeau R, Seney S, Summers K, Chew BH, Denstedt JD, Cadieux PA
Lawson Health Research Institute, University of Western Ontario, London, Canada.
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Objective: To develop a novel in vitro model for the study of bladder and kidney epithelial cell injury akin to stent movement, as ureteric stents are associated with urinary tract complications that can significantly add to patient morbidity. These sequelae may be linked to inflammation triggered by stent-mediated mechanical injury to the urinary tract.
Materials and Methods: T24 bladder and A498 kidney cell line monolayers were damaged mechanically by segments of either Percuflex Plus (PP) or Triumph (triclosan-eluting) stents (both from Boston Scientific Corporation Inc. Natick, MA, USA) and the resulting expression profiles of several pro-inflammatory cytokines and growth factors were analysed.
Results: After control injury using the PP stent, supernatants of both cell lines had significantly increased levels of interleukin (IL)-6, IL-8, basic fibroblast growth factor and platelet-derived growth factor BB, and A498 cells also had increased tumour necrosis factor alpha. In almost all cases, the presence of triclosan within the media abrogated the pro-inflammatory cytokine increases, while its effects on growth factors varied.
Conclusion: This study suggests that stent-related symptoms in the bladder and kidney may be partially due to a local inflammatory response to epithelial damage caused by the presence and movement of the stent. Future stent design should take these inflammatory responses, with respect to physical injury, into consideration, using either more biocompatible materials or anti-inflammatory compounds such as triclosan.

Editorial Comment

The authors have previously evaluated ketorolac coated stents - noting no significant improvement in patient symptoms. It would be of value to test the anti-inflammatory properties of ketorolac-coated stents in this novel in vitro model. It would be interesting to develop epithelial: smooth muscle co-cultured matrices to evaluate the impact of stromal: epithelial interactions following stent irritation on the expression of inflammatory markers and growth factors. The concept of uroepithelial cell disruption as a cause for stent pain may suggest that those patients undergoing long ureteroscopic procedures with forceful irrigation may experience more stent discomfort due to the hydrodistension of the upper collecting system and subsequent stimulation of the inflammatory response. It would be important to evaluate inflammatory markers in urine after ureteroscopy and with urinary stents.

Dr. Manoj Monga
Department of Urology
Cleveland Clinic Foundation
Cleveland, Ohio, USA
E-mail: endourol@yahoo.com

ENDOUROLOGY & LAPAROSCOPY

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Complications of renal cryoablation: a single center experience

Sidana A, Aggarwal P, Feng Z, Georgiades CS, Trock BJ, Rodriguez R
The James Buchanan Brady Urological Institute and Department of Radiology, The Johns Hopkins University School of Medicine, Baltimore, Maryland, USA
J Urol. 2010; 184: 42-7

Purpose: We describe perioperative complications associated with renal cryoablation and identify potential risk factors for certain complications.
Materials and Methods: We retrospectively analyzed the medical records of patients with unifocal renal masses treated with cryosurgery at a single center between 1997 and 2007. All complications associated with these procedures were documented and classified into grades 1 to 5 by the Clavien surgical complication classification. In-depth analysis was done to identify potential risk factors for the most common complications.
Results: We evaluated 101 percutaneous, 52 laparoscopic and 9 open procedures. Complications were noted in 38 procedures (23.5%), including grades 1 to 4 in 19 (11.7%), 8 (4.9%), 5 (3.1%) and 6 (3.7%), respectively, as the severest complication. The most common complication was flank pain (11 procedures), followed by perinephric hematoma and cardiovascular complications (10 each). Mass size ($p = 0.001$), number of cryoablation probes ($p < 0.001$) and chronic anticoagulation ($p < 0.05$) were associated with an increased incidence of significant hematoma. Cardiovascular complications were more common when upper pole lesions were treated, and when an open approach was used (each $p < 0.05$). Respiratory complications occurred in 7 procedures and were associated with patient age ($p < 0.05$) and mass size ($p < 0.01$).
Conclusions: Cryoablation is a relatively safe procedure with a low complications rate in properly selected patients. We identified potential risk factors that may help identify patients most at risk for certain complications and consequently assist in preprocedural planning and counseling.

Editorial Comment

The management of small renal masses has evolved from total removal of the kidney to nephron-sparing surgery. Recently, renal cryoablation has emerged as a new treatment modality for small renal cancer. Although long-term results have not been established yet, it is clear that this novel surgical modality reveals low complication rates when compared to other minimally invasive surgery for management of small renal masses.
Complications were noted in 38 procedures (23.5%) from a total of 162 procedures, including 101 percutaneous, 52 laparoscopic and 9 open procedures. The complications were graded from 1 to 4 in 19 (11.7%), 8 (4.9%), 5 (3.1%) and 6 (3.7%), respectively, as the severest complication.
Interestingly, cardiovascular complications were more common when upper pole lesions were treated, and when an open approach was used (each $p<0.05$); while respiratory complications occurred in 7 procedures and were associated with patient age ($p < 0.05$) and mass size ($p < 0.01$).

Dr. Fernando J. Kim
Chief of Urology, Denver Health Med. Ctr.
Associate Professor, Univ. Colorado Health Sci. Ctr.
Director of Minimally Invasive Urol. Oncology, UCHSC
Denver, Colorado, USA
E-mail: fernando.kim@dhha.org

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Transperitoneal laparoscopic radical nephrectomy for patients with dialysis-dependent end-stage renal disease: an analysis and comparison of perioperative outcome

Bird VG, Shields JM, Aziz M, De Los Santos R, Ayyathurai R, Ciancio G
Department of Urology, Division of Transplantation, University of Miami Miller School of Medicine, Miami, Florida, USA

Urology. 2010; 75: 1335-42

Objectives: To evaluate LRN as treatment for high risk patients. Laparoscopic radical nephrectomy (LRN) is performed for renal tumors not amenable to nephron-sparing treatments. Indications are increasing to include higher risk patients including those with end-stage renal disease (ESRD) necessitating dialysis.
Methods: We performed a retrospective analysis of a patient cohort with clinical stage T1 renal tumors undergoing transperitoneal LRN. Parameters examined included patient demographics, medical comorbidities, tumor characteristics, operative outcomes, and complications.
Results: One hundred eighty-nine patients underwent 195 LRN. Sixteen patients (8.5%) had preexistent ESRD requiring dialysis. A higher American Society of Anesthiologists score (P<.05), higher age-adjusted Charlson comorbidity index (P=.003), higher incidence of previous abdominal surgery (P=.012), and higher incidence of hypertension (P=.025) were found for the ESRD group. Mean blood loss was 153.0 and 132.0 mL (P=.71) in the ESRD patients and non-ESRD patients, respectively. A longer stay (P=.02) was noted for ESRD patients. Mean tumor size in the ESRD patients and non-ESRD patients was 2.6 and 4.2 cm (P<.05), respectively. Renal cell carcinoma was the most common pathology in 14 of 20 (70.0%) ESRD patient renal units and 167 of 175 (95.4%) non-ESRD patient renal units (P=.001). Intraoperative and postoperative complication rates were 6.3% and 31.3% respectively for ESRD patients (P=.05), and 8.7% and 21.4% respectively for non-ESRD patients (P=.35). Most postoperative complications were minor.
Conclusions: LRN, for the treatment of renal tumors in ESRD patients requiring dialysis, is feasible and safe with acceptable intraoperative and postoperative complication rates.

Editorial Comment

Laparoscopic radical nephrectomy (LRN) has become standard of care for renal tumors not amenable to nephron-sparing surgery. LRN is a safe procedure associated with low morbidity for treatment of renal cell carcinoma.

The authors report their experience with LRN as treatment modality for renal masses in high-risk patients. Particularly, patients with end-stage renal disease (ESRD) requiring hemodialysis demonstrated little to no wound complications. Moreover, the authors demonstrated that papillary subtype RCC was more frequent in the ESRD than the non-ESRD population (30% ESRD versus 13.1% of non-ESRD patients).

The transperitoneal laparoscopic approach has shown to be safe and effective to manage high-risk patients with different techniques of CO2 insufflation.

Dr. Fernando J. Kim
Chief of Urology, Denver Health Med. Ctr.
Associate Professor, Univ. Colorado Health Sci. Ctr.
Director of Minimally Invasive Urol. Oncology, UCHSC
Denver, Colorado, USA
E-mail: fernando.kim@dhha.org

IMAGING

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MRI in the characterization and local staging of testicular neoplasms

Tsili AC, Argyropoulou MI, Giannakis D, Sofikitis N, Tsampoulas K
Department of Clinical Radiology, University Hospital of Ioannina, Ioannina, Greece
AJR Am J Roentgenol. 2010 Mar;194(3):682-9.

Objective: The purpose of this study was to assess the role of MRI in the preoperative characterization and local staging of testicular neoplasms.
Subjects and Methods: MRI was performed on 33 patients referred because a testicular mass had been detected clinically and sonographically. Both T1- and T2-weighted sequences were performed with a 1.5-T MRI unit. Gadolinium chelate was administered IV in all cases. We recorded the presence of a lesion and whether the histologic diagnosis of testicular malignancy could have been predicted on the basis of MRI features. For testicular neoplasms, local extension of disease was studied. The MRI findings were correlated with the surgical and histopathologic results.
Results: Histologic examination revealed 36 intratesticular lesions, 28 (78%) of which were malignant and eight benign. Thirteen malignant testicular tumors (46%) were confined within the testis, 12 (43%) had invaded the testicular tunicae or epididymis, and three (11%) had invaded the spermatic cord. The sensitivity and specificity of MRI in differentiating benign from malignant intratesticular lesions were 100% (95% CI, 87.9-100%) and 87.5% (95% CI, 52.9-97.7%). The rate of correspondence between MRI and histologic diagnosis in the local staging of testicular tumors was 92.8% (26/28).
Conclusion: MRI is a good diagnostic tool for the evaluation of testicular disease. It is highly accurate in the preoperative characterization and local staging of testicular neoplasms.

Editorial Comment

High-resolution sonography (US), with color or power Doppler has become the imaging modality of choice for the evaluation of scrotal abnormalities. US is an accurate method in distinguishing intratesticular from extratesticular lesions, a key point in the diagnostic evaluation of scrotal disease. Most intratesticular solid lesions are malignant, whereas extratesticular lesions are usually benign. Although sonography cannot accurately differentiate seminomatous from non-seminomatous tumors, their findings when combined with clinical information allow us to narrow the differential diagnosis of the majority of scrotal masses. Sonography can also be useful for local staging of testicular tumors, although it has limitation for the detection of the invasion of the spermatic cord (1). In such situation, very large scrotal mass or in inclusive sonographic studies, MRI should be performed as a complimentary tool.

The authors of this study nicely show that MRI is an efficient diagnostic tool to evaluate testicular masses and accurately differentiate between benign and malignant intratesticular tumors. With MRI, 87.5% of benign intratesticular mass lesions were characterized correctly. The overall accuracy of MRI in estimating the local extent of malignant testicular tumors was 93%. Contrary to US, MRI was adequate tool for the demonstration of invasion of the spermatic cord by the intratesticular tumor. Unfortunately, similarly to what happens with sonography, focal granulomatous orchitis may also simulate testicular tumor on MRI studies. The authors pointed out one major limitation of this study; they did not compare the diagnostic performances of sonography and MRI in the diagnosing and characterization of testicular disease. Although high-resolution sonography continues to be the imaging modality of choice, MRI is an efficient technique for testicular imaging.

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Dr. Adilson Prando
Head, Department of Radiology and
Diagnostic Imaging, Vera Cruz Hospital
Campinas, São Paulo, Brazil
E-mail: adilson.prando@gmail.com

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Imaging of prostate cancer local recurrences: why and how?

Rouvière O, Vitry T, Lyonnet D
Université de Lyon, Lyon, France
Eur Radiol. 2010; 20: 1254-66.

Objective: Because prostate cancer local recurrences can be efficiently treated by salvage therapies, it becomes critical to detect them early.
Methods: The first alert is the rise of the prostate specific antigen (PSA) level after the post-treatment nadir, which can correspond to a distant recurrence, a local recurrence or both. This so-called biochemical failure (BF) is defined as PSA level > 0.2 ng/ml after radical prostatectomy (RP) and PSA level > nadir + 2 ng/ml after radiotherapy. There is no consensual definition of BF after cryotherapy, high-intensity focused ultrasound (HIFU) ablation or brachytherapy.
Results: Local recurrences after RP are treated by radiotherapy, those after radiotherapy by RP, cryotherapy, brachytherapy or HIFU ablation. Recurrences after cryotherapy or HIFU ablation can be treated by a second session or radiotherapy. Recurrences after brachytherapy are difficult to treat. In patients with BF, MRI can detect local recurrences, whatever the initial treatment was. Dynamic contrast-enhanced MRI seems particularly accurate. The role of spectroscopy remains controversial. Ultrasound-based techniques are less accurate, but this may change with the advent of ultrasonic contrast media.
Conclusion: These recent advances in imaging may improve the outcome of salvage therapies (by improving patient selection and treatment targeting) and should open the way to focal salvage treatments in the near future.

Editorial Comment

The authors should be congratulated for reviewing this important issue on uro-oncology. Important aspects of local recurrence after radical prostatectomy (RP), external-beam radiotherapy (EBRT), HIFU ablation, cryotherapy and brachytherapy are presented and discussed. For each modality of local treatment of prostate cancer, the authors define biochemical failure and discuss treatment options and the role of imaging techniques for the detection of tumor recurrence.

In our experience, dynamic-contrast enhanced MRI is the best modality for the detection of local recurrence after RP. For local recurrence after EBRT our better results are obtained with spectroscopy although dynamic-contrast enhanced MRI can also be useful in most cases. We also prefer to use spectroscopy for the detection of local tumor recurrence after brachytherapy. The quality of dynamic-contrast enhanced MRI stud-

ies in post-brachytherapy glands may be impaired due to the presence of several false-positive results. In our institution we have no experience with MRI for the detection of local tumor recurrence after HIFU ablation or cryotherapy.

Dr. Adilson Prando
Head, Department of Radiology and
Diagnostic Imaging, Vera Cruz Hospital
Campinas, São Paulo, Brazil
E-mail: adilson.prando@gmail.com

PATHOLOGY

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Prostate-specific antigen kinetics during follow-up are an unreliable trigger for intervention in a prostate cancer surveillance program

Ross AE, Loeb S, Landis P, Partin AW, Epstein JI, Kettermann A, Feng Z, Carter HB, Walsh PC
Departments of Urology and Pathology, The Johns Hopkins University School of Medicine, The James Buchanan Brady Urological Institute, The Johns Hopkins Hospital, Baltimore, MD, USA
J Clin Oncol. 2010; 28: 2810-6

Purpose: To assess the predictive ability of prostate-specific antigen (PSA) velocity (PSAV) and doubling time (PSADT) for biopsy progression and adverse pathology at prostatectomy among men with low-risk prostate cancer enrolled on an active-surveillance program.
Methods: We evaluated 290 men who met criteria for active surveillance (ie, PSA density < 0.15 ng/mL/cm(3) and Gleason score < or = 6 with no pattern > or = 4, involving < or = 2 cores with cancer, and < or = 50% involvement of any core by cancer) with two or more serial PSA measurements after diagnosis from 1994 to 2008. Follow-up included twice-yearly digital rectal exam and PSA measurements and yearly surveillance biopsy. Treatment was recommended for biopsy progression (ie, Gleason score > or = 7, or > 2 positive cores, or > 50% core involvement). Sensitivity and specificity of postdiagnostic PSAV and PSADT were explored by using receiver operating characteristic (ROC) analysis.
Results: Overall, 188 (65%) men remained on active surveillance, and 102 (35%) developed biopsy progression at a median follow-up of 2.9 years. PSADT was not significantly associated with subsequent adverse biopsy findings (P = .83), and PSAV was marginally significant (P = .06). No PSAV or PSADT cut point had both high sensitivity and specificity (area under the curve, 0.61 and 0.59, respectively) for biopsy progression. In those who eventually underwent radical prostatectomy, PSAV (P = .79) and PSADT (P = .87) were not associated with the presence of unfavorable surgical pathology.
Conclusion: Postdiagnostic PSA kinetics do not reliably predict adverse pathology and should not be used to replace annual surveillance biopsy for monitoring men on active surveillance.

Editorial Comment

This is an important study concluding that postdiagnostic PSA kinetics do not reliably predict adverse pathology and should not be used to replace annual surveillance biopsy for monitoring men on active surveillance. At Johns Hopkins, the criteria for active surveillance are: PSA density < 0.15 ng/mL/cm3, Gleason score ≤ 6 with no pattern 4 or 5, involving ≤ 2 cores with cancer, and ≤ 50% involvement of any core by cancer (1).

At Stanford, the criteria are: Gleason score ≤ 6 with no pattern 4 or 5, one single core with cancer, linear extent of cancer ≤ 3mm, and serum PSA is not considered (2). It is controversial whether percentage or linear extent is the best measure.

The follow-up included twice-yearly digital rectal exam and PSA measurements and yearly surveillance biopsy. Tretament was recommended for biopsy progression which was considered whenever Gleason score was ≥ 7, > 2 positive cores, or > 50% core involvement. The important finding in Ross et al. study was that PSA double time was not significantly associated with subsequent adverse biopsy findings (p = 0.83) and PSA velocity was marginally significant (p = 0.06).

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Dr. Athanase Billis
Full-Professor of Pathology
State University of Campinas, Unicamp
Campinas, São Paulo, Brazil
E-mail: athanase@fcm.unicamp.br

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The value of mandatory second opinion pathology review of prostate needle biopsy interpretation before radical prostatectomy

Brimo F, Schultz L, Epstein JI
Department of Pathology, The Johns Hopkins Hospital Medical Institutions, Baltimore, Maryland, USA
J Urol. 2010; 184: 126-30

Purpose: We determined the value of mandatory second opinion pathology review to interpret prostate needle biopsy before radical prostatectomy.
Materials and Methods: In all cases referred to our institution for radical prostatectomy in 1 year we compared pathological parameters in original and reviewed pathology reports, including benign, atypical or malignant diagnosis, final Gleason score, positive core number, core highest cancer percent and perineural invasion or extraprostatic extension. A major Gleason score discrepancy was defined as a change to a different risk category (6,7 and 8-10). We defined a significant difference in the highest percent of cancer in a core as 30% or greater.
Results: Of the 855 cases originally diagnosed as prostatic adenocarcinoma cancer was confirmed in 844 (98.8%) by needle biopsy and prostatectomy, of which 9 (1%) were atypical and 2 (0.2%) were benign upon review. A major discrepancy in Gleason score was present in 124 cases (14.7%), of which 57 (46.0%) were upgraded and 67 (54%) were downgraded. Of cases with a final Gleason score of 6, 8.4% were originally diagnosed as 7 (7.8%) or 8-10 (0.6%), 21% with a final score of 7 had an original score of 6 (13.2%) or 8-10 (7.8%) and 21 of 61 (34%) with a score of 8-10 were originally diagnosed as 7 or less. There were 80 cases (64.5%) of disagreement between scores 6 and 7. Of the 777 cases with the positive core number in each

report 71 (9.1%) had discrepancies. After review the positive core number was higher in 45 cases (63.4%) and lower in 26 (36.6%). We noted a significant difference in the highest cancer percent in a core in 76 of 844 evaluable cases (9%) in which cancer was originally underestimated. In 60 of 76 cases (78.9%) cancer discontinuously involved the core on review. Review revealed perineural invasion in 138 of 844 cases (16.3%) that was not originally reported in 37 of 138 (26.8%). In 4 cases review showed extraprostatic extension on needle biopsy.
Conclusions: Compared to a smaller study more than 10 years ago at our institution the rate of unconfirmed cancer was identical (1.2%). To our knowledge this is the first study to analyze concordance upon review of the number of positive cores and maximum percent positive in a core (each discrepancy 9%). In a few cases mandatory second opinion on prostate needle biopsy results in significant differences that may affect therapy.

Editorial Comment

This article by Brimo et al. emphasizes the importance of a second opinion pathology review of prostate needle biopsy interpretation before radical prostatectomy. It may result in significant differences that may affect therapy. Of the 855 cases originally diagnosed as prostatic adenocarcinoma, cancer was confirmed in 844 (98.8%) by needle biopsy and prostatectomy. Therefore, the rate of unconfirmed cancer was 1.2%. Of these unconfirmed cases 1% were "suspicious but not diagnostic" and 0.2% were benign.

The most common benign lesion that simulates adenocarcinoma is partial atrophy. The 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. An additional difficulty in distinguishing cancer from partial atrophy is the positivity for alpha-methylacyl coenzyme A racemase (AMACR) in some acini (2-4).

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Dr. Athanase Billis
Full-Professor of Pathology
State University of Campinas, Unicamp
Campinas, São Paulo, Brazil
E-mail: athanase@fcm.unicamp.br

RECONSTRUCTIVE UROLOGY

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Urethrotomy has a much lower success rate than previously reported

Santucci R, Eisenberg L
Detroit Medical Center and Michigan State College of Osteopathic Medicine, Detroit, Michigan, USA
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Purpose: We evaluated the success rate of direct vision internal urethrotomy as a treatment for simple male urethral strictures.
Materials and Methods: A retrospective chart review was performed on 136 patients who underwent urethrotomy from January 1994 through March 2009. The Kaplan-Meier method was used to analyze stricture-free probability after the first, second, third, fourth and fifth urethrotomy. Patients with complex strictures (36) were excluded from the study for reasons including previous urethroplasty, neophallus or previous radiation, and 24 patients were lost to followup.
Results: Data were available for 76 patients. The stricture-free rate after the first urethrotomy was 8% with a median time to recurrence of 7 months. For the second urethrotomy stricture-free rate was 6% with a median time to recurrence of 9 months. For the third urethrotomy stricture-free rate was 9% with a median time to recurrence of 3 months. For procedures 4 and 5 stricture-free rate was 0% with a median time to recurrence of 20 and 8 months, respectively.
Conclusions: Urethrotomy is a popular treatment for male urethral strictures. However, the performance characteristics are poor. Success rates were no higher than 9% in this series for first or subsequent urethrotomy during the observation period. Most of the patients in this series will be expected to experience failure with longer followup and the expected long-term success rate from any (1 through 5) urethrotomy approach is 0%. Urethrotomy should be considered a temporizing measure until definitive curative reconstruction can be planned.

Editorial Comment

Our understanding of the success rate of optical internal urethrotomy for urethral stricture disease has been primarily based on 2 studies both published in 1996. Pansadoro et al. (1) and Albers et al. (2) were both large retrospective series of optical internal urethrotomy performed with modern techniques. Both showed success rates to be 32-40% with follow-up longer than 24 months. Both demonstrated success to be highest for short segment strictures in the bulbar urethra: 42%1 and 66% (2). Cost effectiveness analysis based on these data has suggested that a single urethrotomy should be attempted before urethroplasty (3). However, primary urethroplasty was preferred if the success rate of urethrotomy was to drop below 35%. Now, the current article by Santucci and Eisenberg demonstrates a much lower success rate for urethrotomy. In fact, the success rate is so low that it begs us to consider whether urethrotomy should be abandoned except in those unable to undergo urethroplasty. How can these data differ so dramatically and which study presents the most accurate assessment of the true success rate for urethrotomy? Several elements of the studies by Pansadoro1 and Albers (2) may have led to an overestimate of the success rate: (1) Several patients in the Albers series were on self-obduration postoperatively (2). Pansadoro et al only included those patients with at least 5 years of follow-up, thus excluding many who may have failed early and then lost to follow-up (3). The follow-up was not well-recorded in the Albers series. So, the article by Santucci and Eisenberg may indeed represent the true success rate of urethrotomy and should serve as a call to others to closely examine the efficacy of an often-performed but poorly-studied procedure.

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Dr. Sean P. Elliott
Department of Urology Surgery
University of Minnesota
Minneapolis, Minnesota, USA
E-mail: selliott@umn.edu

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Morbidity of oral mucosa graft harvesting from a single cheek

Barbagli G, Vallasciani S, Romano G, Fabbri F, Guazzoni G, Lazzeri M
The Centre for Reconstructive Urethral Surgery, Arezzo, Italy.
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Background: The oral mucosa (OM) is a popular substitute for urethroplasty.
Objective: The aim of this study was to investigate oral morbidity and patient satisfaction in a homogeneous group of patients who underwent OM harvesting.
Design, Setting, and Participants: This study is a prospective analysis of 350 patients who underwent OM harvesting from a single cheek.
Intervention: The graft was harvested in an ovoid shape with closure of the wound. Standard graft size was 4cm in length and 2.5cm in width.
Measurements: Self-administered, nonvalidated semiquantitative (0, absence of complications or symptoms; 3, the worst complication or symptom) questionnaire consisting of six questions was used to investigate early complications, with 13 questions designed to investigate late complications and patient satisfaction.
Results and Limitations: Early complications included bleeding, which occurred in 15 patients (4.3%); two patients required immediate surgical revision of the harvesting site. The majority of patients (85.2%) showed no pain, and only 3.7% of patients required use of anti-inflammatory drugs. The majority of patients (65.8%) showed slight or moderate swelling. With respect to late complications, most of the patients (73.4%) reported oral numbness for 1 wk, 22.9% for 1 mo, and 3.77% for 3 mo. Numbness resulting from scarring was absent or slight in most of patients. Changes in oral sensitivity occurred in 2.3% of patients. No difficulties opening the mouth or smiling was found in 98.3% and 99.7% of patients, respectively. Slight or moderate dry mouth was found in 97.1% of patients. In response to the question, "Would you undergo oral mucosa graft harvesting using this technique again," 343 patients (98%) replied "yes," and 7 patients (2%) replied "no."
Conclusions: The harvesting of an OM ovoid graft from a cheek with closure of the wound is a safe procedure with a high patient satisfaction rate.

Editorial Comment

Success rates of substitution urethroplasty with buccal mucosa graft are similar to those using genital skin as the graft material. The principal reason buccal mucosa has been embraced as the graft material of choice is because the graft harvest is believed to cause less morbidity than harvest from other donor areas. Thus, this

article represents an important study documenting the low morbidity of oral graft harvest. The questions asked by the authors cover a broad spectrum of possible symptoms. This confirms most surgeons' observations that oral mucosa harvest is well-tolerated. Still, in the absence of a study that directly compares the morbidity of oral mucosa harvest with that of genital skin harvest it is unclear whether oral mucosa harvest is safer than genital skin harvest.

Dr. Sean P. Elliott
Department of Urology Surgery
University of Minnesota
Minneapolis, Minnesota, USA
E-mail: selliott@umn.edu

UROLOGICAL ONCOLOGY _____

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A new multimodality technique accurately maps the primary lymphatic landing sites of the bladder

Roth B, Wissmeyer MP, Zehnder P, Birkhäuser FD, Thalmann GN, Krause TM, Studer UE
Department of Urology, University of Bern, Bern, Switzerland
Eur Urol. 2010; 57: 205-11

Backgorund: Pathoanatomic studies have failed to map accurately the primary lymphatic landing sites of the urinary bladder.
Objective: To use single-photon emission computed tomography (SPECT) combined with computed tomography (CT) plus intraoperative gamma probe verification to map the primary lymphatic landing sites of the bladder.
Design, Setting, and Participants: Clinical trial of 60 consecutive cystectomy patients at a single centre.
Intervention: Flexible cystoscopy-guided injection of technetium nanocolloid into one of six non-tumour-bearing sites of the bladder for preoperative detection of radioactive lymph nodes (LNs) with SPECT/CT followed by intraoperative verification with a gamma probe. Backup extended pelvic LN dissection (PLND) for ex vivo detection of missed LNs.
Measurements: Three-dimensional projection of each LN site.
Results and Limitations: A median of 4 (range: 1-14) radioactive LNs were detected per site and patient. Ninety-two percent of all LNs were found distal and caudal to where the ureter crosses the common iliac arteries. Eight percent were found proximal to the uretero-iliac crossing, none without simultaneous detection of additional radioactive LNs within the endopelvic region. Extended PLND resected 92% of all primary lymphatic landing sites; limited PLND resected only 52%. A few LNs may have been missed despite preoperative SPECT/CT, intraoperative gamma probe verification, and extended backup PLND.
Conclusions: Multimodality SPECT/CT plus intraoperative gamma probe show the template of the bladder's primary lymphatic landing sites to be larger than is often thought. PLND limited to the ventral portion of the external iliac vessels and obturator fossa removes only about 50% of all primary lymphatic landing sites, whereas extended PLND along the major pelvic vessels, including the internal iliac, external iliac, obturator, and common iliac region up to the uretero-iliac crossing, removes about 90%.

Editorial Comment

The authors of this very interesting study try to answer the question on the extent of lymphadenectomy in bladder cancer surgery on a scientific base. They detect the lymph node landing site of radioactive material injected into several areas of the bladder. Their conclusion is scientifically and clinically sound. As only 8% of "positive" lymph nodes were found cephalad of the uretero-iliac junction, and none of these was without a positive node in the caudal locations very, it is justified to limit the lymphadenectomy to the level where the retracted ureters cross the common iliac vessels. Still, the area to be explored is not "limited" and includes all tissue up to, on, and behind the external and internal iliac vessels and anterior to the presacral space. This paper is recommended reading for all urologic surgeons dealing with invasive bladder cancer.

Dr. Andreas Bohle
Professor of Urology
HELIOS Agnes Karll Hospital
Bad Schwartau, Germany
E-mail: boehle@urologie-bad-schwartau.de

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Transurethral resection of non-muscle-invasive bladder transitional cell cancers with or without 5-aminolevulinic acid under visible and fluorescent light: results of a prospective, randomised, multicentre study

Schumacher MC, Holmäng S, Davidsson T, Friedrich B, Pedersen J, Wiklund NP
Department of Molecular Medicine and Surgery, Karolinska Institutet, Department of Urology, Stockholm, Sweden
Eur Urol. 2010; 57: 293-9

Background: Fluorescent light (FL)-guided cystoscopy induced by 5-aminolevulinic acid (5-ALA) has been reported to detect more tumours compared with standard white-light (WL) cystoscopy. Most reports are from single centres with relatively few patients.
Objective: To evaluate whether 5-ALA-induced FL and WL cystoscopy at transurethral resection (TUR) is superior compared with standard procedures under WL only with respect to tumour recurrence and progression in patients with non-muscle-invasive bladder cancer.
Design, Setting, and Participants: This randomised, multicentre, observer- and pathologist-blinded, prospective phase 3 clinical trial enrolled 300 patients, and of those patients, 153 were randomised to FL cystoscopy and 147 were randomised to standard WL cystoscopy.
Intervention: All patients were first inspected under WL and all lesions were recorded. Patients randomised to FL underwent a second inspection. TUR was carried out in both groups.
Measurements: Control cystoscopy under WL was performed in all patients every 3 mo during the first year after randomisation and biannually thereafter.
Results and Limitations: At the first TUR, the mean number of resection specimens per patient was 2.5 (FL: 2.5; WL: 2.4; p=0.37) and the resulting mean number of resected tumours was 1.7 with FL and 1.8 with WL (p=0.85). More patients were diagnosed with carcinoma in situ (CIS) in the WL group (13%) than in the FL group (4.2%). Within-patient comparison of FL patients only showed that FL detected more lesions than WL. Tumour lesions solely detected by FL cystoscopy that would not otherwise be detected by WL cystoscopy included 52% dysplasia, 33% CIS, 18% papillary neoplasms, 13% pT1, and 7% pTa. Outcome at 12 mo did not show any difference between groups with regard to recurrence-free and progression-free survival rates.

Conclusions: In this prospective, randomised, multi-institutional study, we found no clinical advantage of FL cystoscopy compared with WL cystoscopy and TUR.

Editorial Comment

This paper put some water into the wine of fluorescence-based cystoscopy and resection (TUR). 300 patients from 5 institutions were randomized and the outcome was compared in terms of resected material and, importantly, in terms of clinical outcome after 12 months. In short, no meaningful differences were detected between both groups and the clinical outcomes were similar. The authors argue that the more "positive" results of other groups in favour of fluorescence-based cystoscopy might be due to the monocentric approach of these groups. In conclusion, there is still the need for more objective analyses such as this one before fluorescence-based cystoscopy or TUR can be regarded as standard in urology.

Dr. Andreas Bohle
Professor of Urology
HELIOS Agnes Karll Hospital
Bad Schwartau, Germany
E-mail: boehle@urologie-bad-schwartau.de

NEUROLOGY & FEMALE UROLOGY

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Effect of amitriptyline on symptoms in treatment naïve patients with interstitial cystitis/painful bladder syndrome

Foster HE Jr, Hanno PM, Nickel JC, Payne CK, Mayer RD, Burks DA, Yang CC, Chai TC, Kreder KJ, Peters KM, Lukacz ES, FitzGerald MP, Cen L, Landis JR, Propert KJ, Yang W, Kusek JW, Nyberg LM; Interstitial Cystitis Collaborative Research Network
Department of Surgery, Section of Urology, Yale University, New Haven, Connecticut, USA
J Urol. 2010; 183: 1853-8

Purpose: Amitriptyline is frequently used to treat patients with interstitial cystitis/painful bladder syndrome. The evidence to support this practice is derived mainly from a small, single site clinical trial and case reports.
Materials and Methods: We conducted a multicenter, randomized, double-blind, placebo controlled clinical trial of amitriptyline in subjects with interstitial cystitis/painful bladder syndrome who were naïve to therapy. Study participants in both treatment arms received a standardized education and behavioral modification program. The drug dose was increased during a 6-week period from 10 up to 75 mg once daily. The primary outcome was a patient reported global response assessment of symptom improvement evaluated after 12 weeks of treatment.
Results: A total of 271 subjects were randomized and 231 (85%) provided a global response assessment at 12 weeks of followup. Study participants were primarily women (83%) and white (74%), with a median age of 38 years. In an intent to treat analysis (271) the rate of response of subjects reporting moderate or marked improvement from baseline in the amitriptyline and placebo groups was 55% and 45%, respectively ($p = 0.12$). Of the subgroup of subjects (207) who achieved a drug dose of at least 50 mg, a significantly higher response rate was observed in the amitriptyline group (66%) compared to placebo (47%) ($p = 0.01$).
Conclusions: When all randomized subjects were considered, amitriptyline plus an education and behavioral

modification program did not significantly improve symptoms in treatment naïve patients with interstitial cystitis/painful bladder syndrome. However, amitriptyline may be beneficial in persons who can achieve a daily dose of 50 mg or greater, although this subgroup comparison was not specified in advance.

Editorial Comment

The authors review the efficacy of amitripyline therapy on patients with interstitial cystitis/painful bladder syndrome. All patients treated in this study were naïve to therapy and once enrolled had dose escalation over a six week period up to 75mg per day. All patients while receiving medicine were synchronously enrolled in a behavioral modification program. If the patients withdrew from the study for any reason they were categorized as failures in the post study analysis.

When viewing the study population as a whole, the authors found that there was no significant improvement with the use of amitriptyline plus the behavior modification program over placebo. However, the segment of the group treated with dose escalation to a dose of more than 50 mg of amitryptiline per day had a better than placebo response.

Though these patients faced the onerous symptoms of interstitial cystitis, out of the over 2000 patients contacted, a significant number who passed their screening declined to participate because either they were not interested or had synchronous medical conditions. In addition, those patients in the study who took the placebo still recorded significant adverse events including 31% with constitutional symptoms of fatigue and malaise, 21% having neurologic adverse events consisting of dizziness or somnolence and in approximately one-third pain (primarily headache). That the placebo response was robust at 40% speaks as much as to placebo effect as for the potential efficacy of education and behavioral modification programs in this patient population. This article provides the reader with a clear understanding of the dosage efficacy of amitriptyline for the use of interstitial cystitis if one selects that medication therapy. In addition, the article makes a clear argument for the combination of behavioral modification and education to medical therapy for this patient population.

Dr. Steven P. Petrou
Professor of Urology, Associate Dean
Mayo School of Graduate Medical Education
Jacksonville, Florida, USA
E-mail: petrou.steven@mayo.edu

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Cost analysis of interventions for antimuscarinic refractory patients with overactive bladder

Watanabe JH, Campbell JD, Ravelo A, Chancellor MB, Kowalski J, Sullivan SD
Pharmaceutical Outcomes Research and Policy Program, University of Washington, Seattle, Washington
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Objectives: To estimate average, initial, and cumulative procedure related costs from a US payer perspective extending up to 3 years for the overactive bladder (OAB) interventions: sacral neuromodulation (SNM), intra-detrusor botulinum toxin A (BoNTA), and augmentation cystoplasty (AC) for antimuscarinic refractory patients.

Methods: Costs (2007 US dollars) were calculated using Current Procedural Terminology (CPT) codes, Ambulatory Payment Classification (APC) codes; Diagnosis Related Group (DRG) payments, and Healthcare Common Procedure Coding System (HCPCS) Level II Codes extracted from the literature and from the SNM device manufacturer. CPT codes were converted to costs using the Center for Medicare and Medicaid Services

(CMS) Relative Value Unit (RVU) fee schedule. Sensitivity analyses were performed to evaluate assumptions and uncertainty of results based on plausible variation in estimates of key cost drivers.
Results: The initial treatment cost was $22,226, $1,313, and $10,252 for SNM, intra-detrusor injection of BoNTA, and AC respectively. The first-year cost was $23,614, $2626, and $11,637 respectively. Three years after initiating treatment, the cumulative cost was $26,269, $7651, and $14,337 respectively. Sensitivity analyses revealed that SNM persisted as the most costly intervention in all scenarios. The 3-year cumulative cost range produced by the sensitivity analyses for SNM, BoNTA, and AC was $25,384-$27,357, $4586-$11,476, and $12,315-$16,830, respectively.
Conclusions: All estimates of cost endpoints for SNM were greater than those for BoNTA and AC. These cost estimates, when combined with data on outcomes and risks, are important components of a robust health care technology assessment of antimuscarinic treatment failure options.

Editorial Comment

This article examines the cost of treating one of the most difficult populations with voiding dysfunction, those patients who have failed standard antimuscarinic medical therapy. The authors reviewed three of the most common treatments for this population: sacral neuromodulation, augmentation enterocystoplasty, and intra-detrusor botulinum toxin injections. The cost for the three year therapy was projected and compared among the three therapies.

One of the main challenges of the paper was the cost analysis for projecting the potential cost of botulinum toxin injections in view of its' non-FDA approved status. Regardless, the article makes an illuminating comment regarding the cost of sacral neuromodulation in comparison with the two other therapies. The summary cost of augmentation enterocystoplasty may be somewhat conservative in its estimation in view that the cost of lifelong self-catheterization may not be clearly accounted. Many surgeons who perform this operation understand that a significant segment of those patients treated will need to practice lifelong self intermittent catheterization secondary to their reconstruction. This is currently no small social cost in the United States in view that the self-catheterization is now supported by the government paying for one-time use disposable catheters. The manuscript has a very illustrative graph with projected costs over a time span. It will be interesting to note at what point the projected cost of botulinum toxin-A injections surpasses augmentation enterocystoplasty in overall cost in view of the steeper slope of the botulinum toxin injection line. In addition, the cost of botulinum toxin injections may vary in time with the potential addition of new manufacturers. Regardless, the utility and decreased comparative expense of botulinum toxin injections for this population should surely impress and excite the reader.

Dr. Steven P. Petrou
Professor of Urology, Associate Dean
Mayo School of Graduate Medical Education
Jacksonville, Florida, USA
E-mail: petrou.steven@mayo.edu

PEDIATRIC UROLOGY

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Urinomas protect renal function in posterior urethral valves--a population based study

Wells JM, Mukerji S, Chandran H, Parashar K, McCarthy L
Department of Paediatric Urology, Birmingham Children's Hospital, UK.
J Pediatr Surg. 2010; 45: 407-10

Background/Purpose: Urinomas have been thought to protect renal function in boys with posterior urethral valves (PUVs), although recent reports have disputed this. This study tested the hypothesis that urinomas protect global renal function in boys with PUV.
Methods: A retrospective analysis of all boys with PUV presenting to a tertiary unit derived from a region with an estimated population of 5.5 million was performed. Comparisons of the initial nadir creatinine, current creatinine, and renal status score (RSS) were made between those with and without urinomas. The RSS was derived from nephrology assessment of current renal status (0 = normal to 4 = end-stage renal failure or transplantation). Results were given as median (range), except for RSS, which was given as mean +/- SEM. P < or = .05 was regarded as significant.
Results: During 1989-2009, 9 of 89 PUV boys were diagnosed with urinomas. Initial nadir creatinine was statistically lower in boys with urinomas (31 [18-44] vs 45 [20-574] mumol/L, P < .01). Length of follow-up was similar (5.1 [2.2-17.3] vs 5.9 [1.8-19.7] years, P = .59). Follow-up creatinine was significantly lower in urinoma boys (44 [25-77] vs 61 [29-1227] micromol/L, P < .05), as was the RSS (0.14 +/- 0.14 vs 0.91 +/- 0.14, P < .01). No urinoma boys progressed to end-stage renal failure or required transplant.
Conclusion: This population-based study of PUV boys demonstrates that urinomas reduce nadir creatinine and significantly protect long-term global renal function.

Editorial Comment

The authors reviewed their data on all patients presenting with posterior urethral valves in infancy to their tertiary care center over 20 years. They identified 89 patients, 9 of whom were diagnosed with urinomas. Long term follow-up (mean of 5 years) in 7 of these patients showed that both initial nadir creatinine and follow-up creatinine were significantly lower in boys with urinomas. Renal status score was also significantly better in these boys and none has progressed to end stage renal failure or transplantation. Two of the 9 patients did not have long term follow-up due to their young age.

Spontaneous decompression of the urinary tract in patients with posterior urethral valves has typically been thought to have a protective effect. As the authors point out, this notion has been challenged in the last decade. In response, this population based study is less likely to be tainted by selection bias seen in other reports and supports the hypothesis that decompression has a protective effect on renal function. Unfortunately, this hypothesis has not been uniformly supported by the use of vesicoamniotic shunting in the antenatal period. Perhaps this suggests that there are other factors which create a greater likelihood of spontaneous perforation that serve to protect long term renal function.

M. Chad Wallis
Division of Pediatric Urology
University of Utah
Salt Lake City, Utah, USA
E-mail: chad.wallis@hsc.utah.edu

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Predictive factors for acute renal cortical scintigraphic lesion and ultimate scar formation in children with first febrile urinary tract infection

Oh MM, Cheon J, Kang SH, Park HS, Lee JG, Moon du G
Department of Urology, Korea University Medical Center, Seoul, Korea
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Purpose: We assessed predictive factors for acute renal cortical scintigraphic lesion and ultimate scar formation in children with a first febrile urinary tract infection.
Materials and Methods: A total of 89 girls and 138 boys with a first febrile urinary tract infection were included in the study. We analyzed radiological (ultrasound, dimercapto-succinic acid scintigraphy, voiding cystourethrogram), clinical (age, gender, peak fever, therapeutic delay time) and laboratory (complete blood count with differential count, absolute neutrophil count, blood urea nitrogen, creatinine, urinalysis, Gram's stain, culture, C-reactive protein, erythrocyte sedimentation rate) variables. Dimercapto-succinic acid scintigraphy was performed within 5 days and at 6 months after diagnosis of urinary tract infection. Voiding cystourethrogram was performed after the acute phase of the urinary tract infection. Predictive factors for acute scintigraphic lesion and ultimate scar formation were assessed using logistic regression analysis.
Results: Of 227 patients enrolled 140 had a refluxing and 87 a nonrefluxing urinary tract infection. On logistic regression analysis therapeutic delay time ($p = 0.001$) and presence of reflux ($p = 0.011$) were predictive of acute scintigraphic lesion and ultimate scar formation ($p = 0.001$ and $p = 0.0001$, respectively) in children with a first febrile urinary tract infection.
Conclusions: Since vesicoureteral reflux is the common risk factor for acute scintigraphic lesion and ultimate scar formation, voiding cystourethrogram must be considered as an initial study in patients with acute febrile urinary tract infection.

Editorial Comment

This study examined 227 young children (mean age 9 months) who were hospitalized with their first febrile urinary tract infection. The authors were able to obtain a DMSA renal scan within 1 week of presentation and a subsequent scan at 5 to 7 months on all patients in the study. They also obtained laboratory values at the time of admission and reviewed VCUGs on all patients to determine reflux status. Multivariate logistic regression analysis demonstrated that both the presence of reflux and increased therapeutic delay time were predictive of an acute photon defect on the initial DMSA scan. They were also predictive of ultimate scar formation on follow-up DMSA scans, but the odds ratio was much higher for children with reflux (10.1 vs. 2.4).

The patients in this study were a select population in that they were all young patients and all required hospitalization for their first urinary tract infection. The authors did a nice job getting a complete set of data on their entire study population, which is often a difficult task. The role of imaging studies after urinary tract infections has been challenged in recent years and this study reminds us that reflux status remains a significant risk factor for renal scarring, particularly in this young patient population.

M. Chad Wallis
Division of Pediatric Urology
University of Utah
Salt Lake City, Utah, USA
E-mail: chad.wallis@hsc.utah.edu

Video

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Laparoscopic Sacrocolpopexy for Grade IV Pelvic Organs Prolapse with Associated Bilateral Pyelocaliceal Dilatation: The First Case Reported

Lessandro Curcio, Romolo Guida, Antonio C. Cunha, Juan Renteria, Ricardo Freire, Geraldo Di Biase

Ipanema Federal Hospital (LC, ACC, JR, RF, GDB) and State Civil Servant Hospital (RG), Rio de Janeiro, Brazil

ABSTRACT

Introduction: The main structures involved in maintaining the integrity of the pelvis include the ureterosacral ligament, pubocervical fascia, and the paracervical tissues. A compromise to any of these areas can promote a weakness leading to herniation or prolapse of the urethra, bladder, and/or rectum. Hydronephrosis can range from 5% in first-degree to 40% in patients with third-degree prolapse. A variety of laparoscopic techniques has been described and some have used meshes as an integral part for the repair. This approach aims to restore normal voiding function while preserving female sexual function. Here, we provide a video of a pelvic organ prolapse (POP) female patient with bilateral pyelocaliceal dilation, that was corrected through a laparascopic sacrocolpopexy with mesh technique.
Methods: A 56 year-old female, complained of a ball in your vagina and just evacuated fezzes with aid of the fingers introduced inside the vagina. Her physic exam evidenced a grade 4 pelvic prolapse, bringing down rectum, bladder and urethra and probably kinking bilaterally the ureters, since IVP exam showed a dilated right kidney, almost without function, and the left with a delayed excretion. A laparoscopic correction of the POP was proposed. A 4 ports pneumoperitoneum was utilized. We dissected the retovaginal and bladder vaginal spaces. The mesh was sutured posterolaterally to the distal levator ani muscles, and centrally to central perineum tendon. Anteriorly, the mesh was sutured to the anterior vaginal wall and then passed through the broad ligaments. Both meshes were trimmed and sutured to the anterior longitudinal ligaments of the sacral promontory. The Douglas pouch and peritoneal incision were closed and a transobturator sub-urethral sling was positioned.
Results: The surgery lasted 240 minutes, with a minimum blood loss and just paracetamol was used for postoperative pain. She was discharged in 3 days and her 2 months contrast exam showed pelvic organs in a correct location and better contrast elimination of both kidneys. After a follow up of 12 months, she is continent, with no prolapse recurrence.
Conclusion: Despite some authors contesting the type of access required to correct the pelvic prolapse, undoubtedly the laparoscopic approach provides more anatomic detail, a clear surgical field, better cosmesis, and an early return to physical activity. Moreover, we showed that laparoscopic mesh approach for sacrocolpopexy is feasible, with a minimum morbidity, even in the context of bilateral hydronephrosis secondary to POP. To our knowledge, this is the first published case approached in such a manner in the scientific literature.

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Available at: www.brazjurol.com.br/videos/may_june_2010/Curcio_375_376video.htm

Correspondence address*:*
Dr. Lessandro Curcio
Ipanema Federal Hospital
Av. Ayton Senna, 1850 / 223
22790-700, Rio de Janeiro, RJ, Brazil
E-mail: lessandrocg@ig.com.br

EDITORIAL COMMENT

Curcio et al. have described and shown nice detail pertaining to the Laparoscopic Sacrocolpopexy for Grade IV pelvic organ prolapse. The authors also delineate the relationship between the presence of preoperative bilateral pyelocaliceal dilation and the subsequent resolution postoperatively. This observation is somewhat novel.

A nice review of the pertinent anatomy and technique is explained both in the written abstract as well as in the video. Finally, technical points of the actual repair are clear, concise and the satisfactory postoperative information is reported.

Dr. Rafael E. Carrion
Associate Professor of Urology
Department of Urology
USF Health College of Medicine
Tampa, Florida, USA
E-mail: rcarrion@health.usf.edu