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Penile Cancer: The Importance to predict lymph node metastasis

The November-December 2016 issue of the International Braz J Urol presents original contributions with a lot of interesting papers in different fields: Bladder Cancer, BPH, Prostate Cancer, Renal stones, Renal Cell Carcinoma, Pediatric Urology, Peyronie Disease, Erectile Disfunction, Penile Cancer, Testicular torsion, Hypogonadism, and Hemorrhagic cystitis. The papers come from many different countries such as Brazil, USA, Turkey, India, China, Iran, UK, Netherlands, Germany, Pakistan and Chile, and as usual the editor's comment highlights some papers. We decided to comment the paper about a very usual topic in Brazil: Penile Cancer.

Doctor Aita and collegues from Brazil performed on page 1136 an interesting study about the prognostic factor in penile cancer. The authors evaluated some prognostic factors for global survival (GS) and cancer-specific survival (CSS) in a historical series of patients with penile cancer not submitted to lymphadenectomy and that did not show lymph node metastasis in a minimum follow-up of three years. The authors evaluated the clinical and pathologic characteristics of 163 patients with penile carcinoma and clinically negative inguinal lymph nodes followed for three or more years and their impact on global survival (GS) and cancer-specific survival (CSS) in the 10-year follow--up. Primary pathologic tumor stage (p=0.025) and the presence of high grade of tumor differentiation (p=0.018) were predictive of CSS. The presence of high grade tumor was an independent specific prognostic factor of death risk (RR 14.08; p=0.019). The authors concluded that a high histologic grade was an independent predictive factor of specific death risk in patients with penile carcinoma and clinically negative lymph nodes followed for three or more years.

Penile cancer is a rare neoplasia with low incidence in developed countries. In Brazil the incidence rate of penile cancer is 2.9 - 6.8/100,000 inhabitants, resulting in this country having one of the world's highest incidence rates for this neoplasia (1, 2). The most common sites of penile cancer metastasis are the superficial and deeper nodes of the inguinal and iliac region. Patients have inguinal groin masses in 58% of cases, and 40% have positive metastasis, even in small cancers such as T1C and T2 (3).

Penile lymphatic drainage parallels venous drainage, with a superficial system that drains the skin and a deeper system that drains the glans and corporal bodies. The superficial inguinal nodes are located just below the inguinal ligament and extend trough 4-5 cm of the saphenous hiatus. They are distributed in quarters set from the anastomosis between the saphena magna and femoral veins (4). The deeper inguinal nodes are located just below the fascia lata and medially to the saphena vein. Although small in number, these nodes are of extreme importance, since their venous drainage occurs through the superficial iliac veins (4). Extended Inguinal lymphadenectomy is the most

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useful and commonly performed surgery for staging and to cure inguinal metastasis in penile cancer cases. Although it is a widespread technique, post operatory complications often occur (3).

In the paper commented here we observed a interesting conclusion. The patients not submitted to inguinal lymphadenectomy and that did not regionally progress after three years, a small subgroup of patients died due to cancer. Main independent prognostic factor for CSS was the presence of high grade primary tumor. Patients not operated but with high grade tumors that refuse surgery comprise a high risk group and require a more diligent follow-up. The high histologic grade remains a risk factor for death due to penile carcinoma, even in sub-groups without lymph node metastasis. The great question in the treatment of penile cancer is: When we need to make the lymphadenectomy? This paper is very interesting and can help with this question in future researches.

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EDITORIAL

Data vs Dogma in Peyronie's Disease

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Curvature of the erect penis from elements of internal fibrosis has been recognized for centuries (first described in 1743), yet our understanding still seems limited. Guidelines exist in both the United States and Europe, with most based on low level evidence and opinion (1, 2). Men afflicted by this situation are typically lumped together and labeled with the singular descriptor of Peyronie's disease. The level of evidence for the pathophysiology and natural history of this affliction is poor, as is the awareness of data surrounding treatment modalities. This is evidenced by the fact that one of the most commonly provided interventions is Vitamin E, which has not been shown to provide benefit and is not recommended by existing guidelines. In medical practice, it is dangerous to equate shared assumptions with fact, as this may limit pursuit of additional knowledge. Additionally, in the absence of evidence, logic should prevail.

The moniker of Peyronie's disease implies that the patient is clinically affected (thus a state of disease) rather than palpable, yet asymptomatic induration of the penile shaft. This term is used by providers to describe anatomical distortion of the penis from fibrosis. The concept of genetic predisposition has been suggested based on concomitant appreciation with Dupuytren's contracture, but this is unproven. As retrospective studies consistently note that the most common etiology is idiopathic, and considering that patient presentations are variable, it seems likely that there are multiple sets of circumstances that may produce this symptom complex rather than all men manifesting a shared underlying condition.

The fibrosis seen in many patients is similar to the injury response seen in other parts of the body. Consider the familiar sounding tale of myositis ossificans whereby repetitive trauma leads to ectopic calcification within a muscle. King provides a detailed description that involves an acute and mature phase, "loss of stretch", and the "potential to cause pain and loss of function" (3). Stretch therapy has not been found to be helpful for this condition, and agents like indomethacin have been used in the absence of evidence. The concept has been put forth that recurrent injury results from premature return to activity. The similarities between such description and clinical experience with Peyronie's disease should be obvious to the sexual health professional.

A commonly suggested mechanism for development of a penile plaque is repetitive microtrauma from sexual activity that results in disruption of the tunica albuginea followed by a dysregulated healing response culminating in excess collagen deposition (1, 2). This seems problematic based on logic. If one considers the usual scenario of heterosexual vaginal intercourse, the most commonly applied forces to the penis result in dorsal flexion. In this state, the convex (i.e., ventral) side has increased tension, whereas the concave (i.e., dorsal) side has decreased tension. This explains why corporal disruptions in penile fractures are commonly noted on the ventral tunica, and this phenomenon is analogous to a greenstick fracture in children. Thus, it would seem more logical that the process may be due to damaged cavernosal

tissue that induces a fibrotic reaction that secondarily involves the overlying tunica albuginea, akin to activating a 'glow-stick'.

Occasionally, men will be seen with ventral curvature that is not congenital in nature. Some will describe sudden development after being discharged after a hospitalization involving an indwelling Foley catheter. It is conceivable that patients may have unconscious erections despite catheterization, and that the penis may not extend in a natural and comfortable manner with a firmly secured catheter dry enough to where friction precludes sliding of the urethra over the surface. Likewise, I have seen patients present with ventral curvature following aggressive direct vision internal urethrotomy of bulbar strictures. Despite the spongiosum being thinnest at 12 o'clock, many providers still insist on cutting at this location during DVIU, often to the point of observed bleeding. This may easily represent passage through the tunica of the urethra to the level of the septum. So, while these men may have iatrogenically induced fibrosis within the penis, once curvature develops, they will be classified as having Peyronie's disease.

The dogmatic approach to timing of intervention with Peyronie's disease has been to wait for resolution of pain and stabilization of curvature. It seems logical to assume that the pain is secondary to inflammation, common to the wound-healing response. It also seems somewhat logical that one wouldn't want to surgically intervene for curvature if there was a reasonable chance that further curvature was inevitable and could be better managed by delaying the operation. However, once a penis begins to take on curvature, most commonly dorsal in nature, the penis would seem more prone to flexion based trauma. Similarly, patients with less turgid erections are more subject to such forces and resultant elastic tissue fatigue that may lead to additional rupture of fibers and multiple scars. Thus, it could also reasonably be asserted that earlier stabilization of curvature may limit the extent of damage and the ultimate degree of distortion. Whether this would be best accomplished by plication or use of PDE5Is to improve rigidity and limit the flexibility of the erect penis is unclear. Also, research evaluating the therapeutic potential of PDE5Is based on antifibrotic properties seems confounded by the benefit of improved axial stability. The AUA guidelines state that "surgical outcomes for patients with active disease are not known" (statement 17) (1). If one considers the situation of penile fracture, it is generally regarded that non-operative management is ill-advised. Although perhaps not as clinically severe or acute in presentation, the ongoing injury involved in stimulating penile plaque formation may exist along the same spectrum.

Diagnosis of a problem can be made based on a patient's history. The degree of the problem can be characterized by physical examination and documentation of the level of curvature. Although penile duplex studies are used by some providers, there is no evidence that the results change physician decision-making, although it is conceivable that it may affect patient perception.

Within the AUA guidelines, it is important to note that no treatments options are supported by Grade A evidence. Of the available treatment modalities, the only agent approved by the FDA is collagenase Clostridium histolyticum (CCH). This is felt to be an option for patients with stable dorsal curvature of 30-90 degrees in the absence of erectile dysfunction. The guidelines state that intralesional interferon or verapamil can be considered, but notes that the "evidence for efficacy is weak". In vitro data shows that verapamil decreases fibroblast proliferation and encourages degradation of collagen, rather than production. Thus, proponents of intralesional injection (ILI) argue that it is "reasonable and scientifically sensible" and some data has shown reduced pain and curvature in 30-60% of men after 12 injections over 6 months (4). However, the data is quite poor. Russell et al reviewed the literature in 2006, noting 19

studies, 17 of which reported positive results (5). These studies included use of steroids, CCH, verapamil, and interferon. Oxford criteria was applied to grade the evidence from strongest (1) to weakest (5), and 16/19 (84%) were level 4, with the only level 1 study involving a multicenter study of interferon that found no improvement in sexual function (6).

It seems that if the positive results are to be believed, the common denominator in these studies is not the drug, but the needle. Consider the outcomes with normal saline (NS), which has shown statistically significant improvement in curvature, with nicardipine doing no better (7). When compared to verapamil in electromotive therapy in a double blinded study, there was no significant difference (8). In the only level 1 study on ILI mentioned earlier, NS showed statistically significant improvements in curvature, plaque size, and plaque density (6). In nearly all of the articles published, full disclosure of injection technique is lacking. In fact, many providers will pass the needle back and forth through the plaque numerous times, essentially rendering this minimally-invasive surgery by needle fracture. Given the absence of ultrasound guidance in most cases and the practical limitations of using a small gauge needle to force fluid to spread through an extremely dense (and occasionally calcified) laminar plaque, it is not surprising that we have demonstrated to senior providers (with ultrasound) that when they thought the needle was inside the plaque, it was well within the corpora cavernosum.

CCH was approved for ILI based on two randomized, multicenter, double-blind placebo-controlled trials involving 832 patients with dorsal curvature, no calcifications, and 'stable' disease (9). On average, patients were 57 y/o, with 4 years of curvature that averaged 50 degrees, and 50% had ED. Comparing baseline to patient status at 52 weeks, patients treated with CCH improved from 48.8 to 31 degrees, and those given NS improved from 49 to 39 degrees. In the second study, the CCH group improved from 51.3 to 35.1 degrees, while the NS group improved from 49.6 to 41.1 degrees. The difference was reported as statistically significant, but this was calculated based on percent change and not the absolute improvement in number of degrees. Perspective seems important here. Many experts have identified 30 degrees as the point of problematic curvature, which is reflected in the trial design (but may also be somewhat dogmatic). At the end of both trials, both arms still had a final average curvature greater than 30 degrees. Additionally, CCH reduced curvature by 17% more than NS in Study 1 and 11% in Study 2. With the average curvature of about 50 degrees, this amounts to an additional improvement of 5.5-8.5 degrees for $26,429 in the US, which is 9x more expensive than plication (10). Also, if one looks closely at the 2nd study, the improvement bottoms out at 42 weeks and starts worsening again by 52 weeks (end of study). This suggests the possibility that patient curvature may be returning toward baseline. Data was presented at the 2016 AUA Annual Meeting on 78 patients who completed 4 cycles of CCH, with curvature changing from 58.5 to 42.0 degrees (11). Only 6/78 men had restoration of the ability to engage in intercourse and 33% had glans hypoesthesia. In the initial studies, 92% of patients had at least one adverse reaction, but corporal rupture was rare (9). However, a recent survey of urologists noted that 34% had witnessed this complication in practice, typically around 5 days after the last CCH injection (12).

The threats to male sexual function are numerous. Nearly half of men with PD have mild or moderate depression (13). Erectile function typically worsens with age, and time stops for no man. The panel for the AUA guidelines asserted that ineffective therapies that postpone return to sexual activity places a moderate burden on the patient (1). For a man eager to return to regular sexual activity, a therapeutic approach that involves a year of his life and is unlikely to result in a state that experts define as below

a problematic cutoff seems ill-advised. Dogma should be perpetually challenged in medicine. In regard to PD, despite traditional mantra advocating stability of curvature before correction, a logical argument can be made for early intervention and restoration of rigidity. The often asserted mechanism of dorsal tunical disruption as the initiator of disease should be questioned. Transparency is needed in descriptions of technique related to ILI, and NS should no longer be considered a placebo and ILI should be viewed as surgical therapy via needle fracture. CCH therapy, when viewed with practical perspective, seems to be of limited value. Cease and desist letters may be need to stop providers from using ineffective topical and oral therapies.

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DIFFERENCE OF OPINION

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MRI should be routine for all patients with localized prostate cancer? | *Opinion: Yes*

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Keywords: Magnetic Resonance Imaging; Prostatic Neoplasms; Diagnosis; Watchful Waiting

Magnetic resonance imaging (MRI) has been used for staging prostate cancer (PCa) since the 1990's, more precisely after the advent of the endorectal coil, which enabled significant improvement in the quality of the examination. Also, the standardization of prostate MRI with multiparametric sequences (including high resolution T2-weighted, diffusion and dynamic contrast-enhanced or perfusion images), together with the progressive learning curve by uro-radiologists, contributed to include the method definitively in the list of available procedures for staging prostate cancer (1).

The accuracy of multiparametric MRI (mpMRI) is greater than that of other isolated clinical, laboratory and imaging methods available, with specificities around 85% for detection of extracapsular extension and seminal vesicle invasion (2). Moreover, the incremental value of MRI has been validated around a decade ago in three articles by the interdisciplinary group of Memorial Sloan Kettering Cancer Center, demonstrating that the addition of MRI to the commonly used clinical nomograms significantly increases the accuracy for prediction of organ-confined disease, extracapsular extension and seminal vesicle invasion (3-5).

The indication and acceptance of mpMRI for prostate cancer staging increased after the development and clinical use of 3 Tesla (T) scanners (which have twice the magnet field strength in comparison to more common 1.5 T scanners), allowing the achievement of multiparametric studies of the prostate without the need for an endorectal coil, with the same resolution and image quality as compared to the studies on 1.5 T scanners with endorectal coil (6).

On the other hand, performing mpMRI for staging of PCa after the biopsy has some limitations. First, a recent meta-analysis with a very large number of studies and patients, evaluating the performance of MRI for local staging of disease, showed high specificities (88-96%) but low sensitivities (57-61%), considering that microscopic infiltration of the capsule or seminal vesicles might be undetectable even with state-of-the-art equipments and protocols (7). Also, there must be a minimum interval of three weeks between prostate biopsy and MRI, to minimize bleeding artifacts that impair the interpretation of the study (8). Finally, it is arguable that very-low and low risk tumors would not benefit from a staging mpMRI, since the chance of extraprostatic disease is small (9).

In this decade, a new and promising application for MRI has emerged: by using standardized interpretation and reporting systems (like PI-RADS and Likert), mpMRI can be used as an additional screening tool to stratify the risk for prostate cancer. mpMRI has the ability

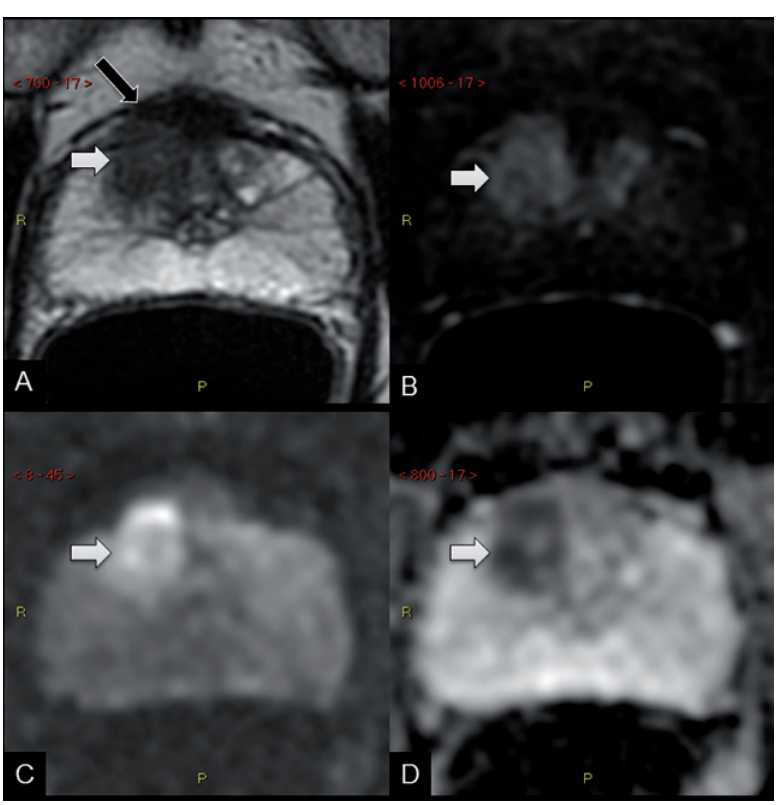
to detect small clinically significant tumors in areas that might go undetected on a standardized, random biopsy; on the other hand, clinically insignificant tumors are usually not seen on mpMRI. A recent meta-analysis has shown pooled sensitivities and specificities of 82% for prostate cancer detection in articles that accurately used the PI-RADS criteria (10).

The digital images obtained on mpMRI can be used to improve ultrasound (US) guided biopsy procedures by using MRI-US fusion techniques, whether cognitive (when the radiologist or urologist visually defines the region of the suspected lesion on mpMR images and directs additional fragments to this region) or real-time (when the digital mpMR images are uploaded in the US equipment and allow real-time visualization of the concordant MR and US images during the biopsy). Many recent articles have demonstrated that, in comparison to random biopsy, fusion biopsy techniques improve in up to 30% the detection of clinically significant PCa (reducing disease morbidity and mortality), while decreasing the detection of insignificant disease (reducing overtreatment) (11, 12).

By performing mpMRI prior to biopsy, a paradigm-shift is evolving, since lesions highly suspicious for clinically significant tumors are been locally staged by mpMRI before histological confirmation of the disease. This may sound unorthodox, given the historical algorithm of prostate cancer detection and staging, but is the usual workflow in many other tumors (such as kidney cancer), and might increases the capability of the radiologist to locally stage the disease in prostates without biopsy-related artifacts (Figure-1).

Although mpMRI has been currently used for PCa detection in many centers, the definitive incor-

Figure 1 - 59 years old man, elevated PSA (8 ng/mL), no prior biopsy. mpMRI performed on a 3 Tesla scanner without an endorectal coil revealed a focal lesion of the right anterior transition zone of the prostate (white arrows), with homogeneous low signal intensity on the T2-weighted images (A), early enhancement on the dynamic post-contrast sequence (B), marked restricted diffusion on the diffusion-weighted (C) and ADC sequences (D), and suggestive signs of infiltration of the fibromuscular stroma and extension to the periprostatic fat (black arrow), highly suspicious for prostate cancer (PI-RADS 5). Real-time MR/US fusion biopsy confimed a Gleason 7 (4+3) tumor in this area, and prostatectomy revealed a Gleason 8 (4+4) pT3a lesion.



poration of mpMRI in the screening algorithm of PCa in the general male population is still restricted by relevant issues: the exam is costly and time-consuming, the availability of 3-Tesla scanners is limited, and the need of contrast-injection for the perfusion part of the protocol carries the (small) risk of allergic reactions and other rare side-effects. Therefore, many center are investing on faster, cheaper, non-invasive and harmless MR protocols for PCa screening, generically called bi-parametric MRI (since it includes only T2 and diffusion-weighted sequences), which can perform on more widely available 1.5 Tesla scanners without an endorectal coil. Two recent articles demonstrated a good accuracy of bi-parametric MRI, associated with serum-PSA levels, for the detection of PCa in correlation to biopsy (13, 14).

In conclusion, mpMRI has already been accepted as a valuable method for local staging in patients with intermediate to high-risk PCa. However, given the growing applicability of mpMRI for the screening of clinically significant tumors (and supported by some urologists' perspectives on prostate cancer imaging (15)), I would humbly suggest a rephrasing of the proposed theme of this article: in the near future, all men with suspicion for prostate cancer should undergo MRI.

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DIFFERENCE OF OPINION

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MRI should be routine for all patients with localized prostate cancer? | *Opinion: No*

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Keywords: Magnetic Resonance Imaging; Prostatic Neoplasms; Diagnosis; Watchful Waiting

One of the basic principles of medical care is that a diagnostic test should inform a clinical decision. If the test is uninformative, it is not useful; if no decision is to be made then a diagnostic test is not necessary. Indeed, performing a diagnostic test when it adds nothing to the decision-making process is not only a waste of healthcare resources, it is potentially harmful, leading to incorrect conclusions or more unnecessary testing. From this perspective, how could mp-MRI potentially inform the initial management of localized prostate cancer?

Men who are candidates for active surveillance based on low-risk prostate cancer (cT1c, PSA<10, Grade Group 1 (Gleason 3+3=6)) may be harboring a higher grade tumor that eluded the initial biopsy, particularly if it is anteriorly placed. mp-MRI has the promise of detecting this potentially more serious cancer and avoiding the risk of inappropriate observation. Some have argued men with low-risk prostate cancer with a "normal" mp-MRI (PI-RADS 1) have very little risk of cancer progression. The promise of mp-MRI to provide a better risk assessment in men considering active surveillance is alluring.

Unfortunately, the evidence that mp-MRI used in the initial assessment of clinically localized prostate cancer to improve the outcome of men undergoing active surveillance is lacking. The slow growth of prostate cancer means that even higher grade cancer will become clinical evident, with or without an MRI. Metastatic or lethal prostate cancer in the largest active surveillance cohorts—mostly selected without mp-MRI—are rare events (1). It appears readily available clinical features like PSA, grade and stage are adequate in almost all cases to determine who can safely start down the path of active surveillance. Although a "normal" mp-MRI may be reassuring to a patient and/or their physician it actually adds very little to the decision-making process.

The local staging of prostate cancer based on a digital rectal exam (DRE), which only assesses the posterior aspect of the gland, could be enhanced by the whole-gland assessment provide by mp-MRI. Certainly it is better to know the location, size and extent of the cancer before considering treatment. This information can determine whether the cancer is surgically resectable and guide surgical approach, particularly in the decision to preserve neurovascular tissues. It could also guide a focal therapeutic approach. The improved staging provided by mp-MRI make it an attractive test to obtain in the initial assessment of clinically localized prostate cancer.

Unfortunately, mp-MRI is not as nearly as attractive as promised in prostate cancer staging. First, prostate cancer is distinguished by multifocality within the gland. The accuracy of mp-MRI to find all the prostate cancers is woeful. Using the gold-standard of whole-mount histopathology compared to preoperative mp-MRI, the overall sensitivity of mp-MRI to detect tumors was 47% (2). Sensitivity improved to 72% for tumors over 1 cm or with Gleason score ≥7, and up to 80% for the index tumors. Prostate cancers less than 5 mm in diameter are essentially invisible on mp-MRI. As a staging test, mp-MRI is only useful for lesions it can detect: the remainder the gland remains a clinical black box. Second, accurate staging requires defining the extent of an infiltrating cancer. The accuracy of mp-MRI to locate the edge of a cancer is awful. It systematically underestimates histologically determined tumor boundaries. This is particularly true for the most clinically concerning cancers, those with a high imaging suspicion score and high Gleason score (3). This is why focal therapy based on mp-MRI is not nearly as focal as it could be, as a 9 mm treatment margin is advocated with focal therapies to ensure successful treatment of the entire tumor (3). Others have shown prostate cancer foci are an average 11 mm longer and have a volume 3 times greater than estimated by MRI (4). Again, as a staging test, mp-MRI comes up short. Third, the defining the presence of extracapsular extension (ECE) can directly influence a therapeutic approach. Here, mp-MRI has consistently demonstrated high specificity, in the 90% range (5). If one suspects ECE on mp-MRI there is a high likelihood it will be present on final pathological assessment of the specimen. Unfortunately, mp-MRI has very poor sensitivity to detect histological ECE, roughly 50% (5). There is no assurance ECE is not present when the mp-MRI doesn't detect it. Overall, as a staging test, mp-MRI is far from attractive: "homely" would be a better descriptor.

Zealots for mp-MRI in the management of prostate cancer have suggested it has the ability to grade the cancer, or at least distinguish between low-risk (Gleason score 6) and higher-risk (Gleason score 7, 8 and 9) tumors. Although low-risk tumors have higher ADCs than higher risk tumors, the ADC overlap between Gleason score 6 and Gleason score 7 cancers is significant: roughly half of Gleason scores 7 cancers have ADCs that are indistinguishable from Gleason score 6 cancers (6). Furthermore, the ranges of ADC between roughly half of Gleason score 7 and all Gleason score 8 and 9 cancers are overlapping. By far, the most accurate assessment of grade is by histology, not radiology.

Another problem of mp-MRI for prostate cancer is the significant challenge of accurate interpretation. The literature is replete with examples of the variability of radiologists to assess prostate cancer using mp-MRI (7, 8). The learning curve appears to be steep and long: this is not a skill acquired easily. Unless prostate mp-MRI becomes a standard test in all cases of prostate cancer—a dubious goal given the points articulated above—it is reasonable to question whether there will be enough informative cases to train the world of radiologists to interpret them. Furthermore, using the current mp-MRI technology, it seems the limits of this test have been reached. The visual and cognitive challenge for a radiologist to accurately define prostate cancer will only be as good as the mp-MRI images that routinely fail to detect, define and characterize prostate cancer.

Value in healthcare has been defined as the outcome divided by the cost (9). Outcomes of men with prostate cancer must be demonstrably improved by introducing the additional expense of mp-MRI for that technology to be considered of value. Frankly, I see almost no evidence mp-MRI has improved the outcome of population of patients with prostate cancer.

Accepting that mp-MRI may not be useful in every man with clinically localized prostate cancer, isn't there a role in selected patients, particularly when it may directly influence a surgical approach? In my opinion, the answer to this question must be based on an honest assessment of the outcomes of one's own surgical series and clinical experience as opposed to practice patterns the field. This is admittedly the least scientifically approach to answering the question, but it is also the most applicable to the next patient presenting to me as a surgeon. If including mp-MRI in the initial assessment of that patient will improve his eventual outcome, it should be obtained: if it will not, then it adds nothing.

I only perform open radical retropubic prostatectomies, so my thoughts about surgical approach may not be applicable to those using a minimally-invasive approach. First, decisions about the resectability of a prostate cancer have reliably been based on DRE. Unresectable tumors—those invading the levators or distal urethra—are obvious. An mp-MRI would only confirm what is already known by physical exam. Very rarely have I encountered

cancer grossly invading the bladder intraoperatively; although mp-MRI may have been useful in avoiding surgery in those handful of cases, it certainly does not justify obtaining imaging even in selected cases. Furthermore, since I routinely widely resect the bladder neck, any positive margin at that location is microscopic and are invisible to mp-MRI. Second, the need to perform a wider resection of the neurovascular bundle in an area of suspected ECE is not a mystery. Preoperative DRE and inter-operative assessments are rarely misleading. Third, even if mp-MRI suggests ECE, clinical T3 disease does not equate to surgical futility. Men with pT3 disease can still be cured with radical prostatectomy and mp--MRI should not dissuade taking that approach. Indeed, in my series of 3000 consecutive open radical prostatectomies, the percent of non-organ confined cancers has increased significantly (Figure-1). Despite more locally invasive disease, the frequency of bilateral nerve-sparing procedures remains over 90% (Figure-2). How? Because for the last 1200 cases, the overall positive surgical margin rate has been under 5% (6.7% for the entire series) (Figure-3). With experience and meticulous attention visual and haptic cues, the positive surgical margin rate for pT3 diseases has been less than 15% for the last 1200 cases. Only a fraction of these patients underwent an mp-MRI prior to surgery (obtained by another physician) and in no case did the result of that study influence the operative approach. Based on this experience, I tell my patients who are candidates for a radical prostatectomy that mp-MRI plays no role in the clinical decision-making process.

I hope my comments will quickly become of historic interest only, as better imaging techniques overcome the current short-comings of mp-MRI and allow precise cancer localization and characterization. This will make whole-gland focused therapies largely obsolete and allow us to observe the majority of prostate cancers that are of no threat.

Figure 1 - Percent of non-organ confined prostate cancer in 3000 consecutive patients undergoing open radical retropubic prostatectomy by a single surgeon (JBN).

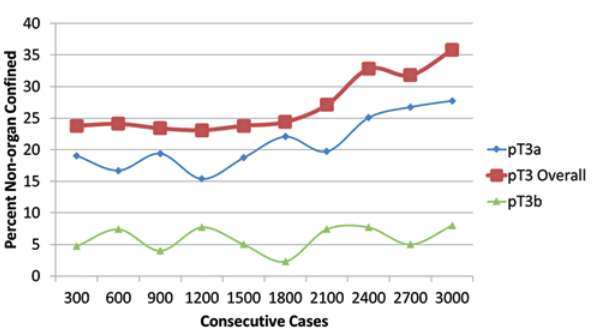


Figure 2 - Frequency of bilateral nerve-sparing procedures in 3000 consecutive patients undergoing open radical retropubic prostatectomy by a single surgeon (JBN).

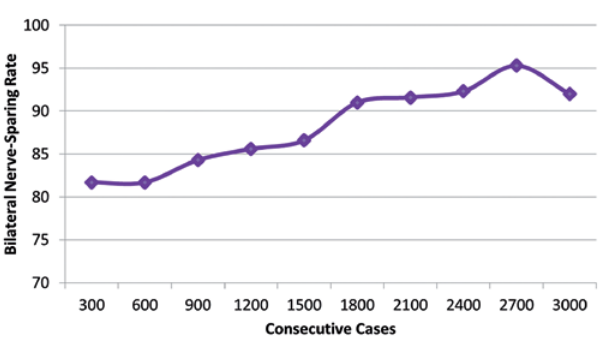
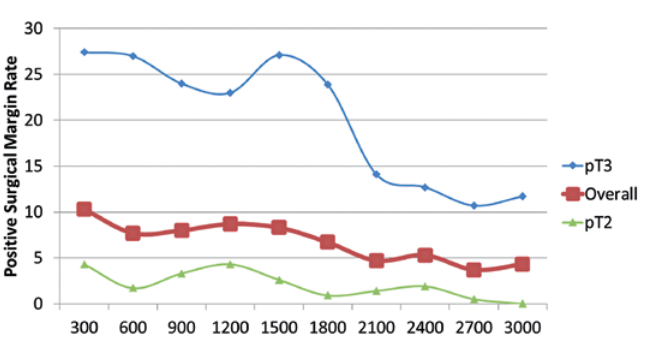


Figure 3 - Rates of positive surgical margins in 3000 consecutive patients undergoing open radical retropubic prostatectomy by a single surgeon (JBN).



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REVIEW ARTICLE

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Prostate cancer screening in Brazil: should it be done or not?

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ABSTRACT

The use of PSA in the screening, detection and prognosis of prostate cancer (PCa) has revolutionized the diagnosis and treatment of this disorder with an increase in detection rates and PCa organ-confined. Despite these benefits and ease of implementation, tracking PCa remains a matter of great controversy. We conducted a literature review and demographic and epidemiological data in Brazil feeling to assess the current state of screening and whether there is justification for population programs. the differences are valued between developed and underdeveloped countries as the incidence, mortality, screening and access to health. an analysis of the advantages and disadvantages of screening is made as well as a critical analysis of existing studies on screening and some recommendations on a rational screening.

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Prostatic Neoplasms; Mass Screening; Brazil

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INTRODUCTION

The use of prostatic specific antigen (PSA) for screening, detection and prognosis of prostate cancer (PCa) had a big impact on diagnosis and treatment of this disease. It was observed an increase of detection rate, and particularly an tremendous increase of detection of organ-confined disease (1-5). From 1986 to 1993, the incidence of PCa increased from 86 to 179 cases/100.000 white men and from 124 to 250 in black men. The rate of metastasis at diagnosis dropped from 15 to 6.6 cases/100.000 (6). Although with clear benefits and easy to perform, PCa screening is very controversial. In the north hemisphere countries, where screening protocols were applied at populations at risk, it was observed an initial reduction of morbidity and mortality rates followed by a stagnation of these rates. This epidemiologic kinetics, although with low level of evidence, lead the American Urological Society to not recommend the use of vast screening of risk groups in North America (7).

The recommendation was based on a decision of the United States Preventive Services Task Force (USPSTF) (8) (grade D recommendation) mainly based on the contrary results of two major studies: European Randomized Study of Screening for Prostate Cancer (ERSPC) (1) and Prostate, Lung, Colorectal, and Ovary Cancer Screening Trial (PLCO) (9). That recommendation need to be

worldwide validated. PCa screening rate (SPCa) is higher in comparison in USA and western Europe than in other countries, where it has been applied systematically (10). In under-developed countries, such as Brazil, there are no government SPCa rates and the numbers are opportunistic, according to information of population studies derived from isolated municipal campaigns (11). In 2008, it was estimated that there were 899.000 new cases of PCa documented in the World and 258.000 deaths. The estimate for 2030 is 1.7 million cases with 500.000 deaths (12).

Internationally, it is observed a wide range of incidence and mortality rates, mainly due to early diagnosis based on PSA screening. Variation of incidence among countries may be up to 24 times and of mortality of up to 10 times (12). It is important to correlate those data with other populations, in particular in less developed countries, with different ethnic background and economical status, in a different historical moment in terms of SPCa.

We performed a literature review of demographic and epidemiologic data from Brazil in order to evaluate the current status of SPCa trying to stablish the need or not of population screening programs. This review may provide data for government and medical societies decisions for screening programs for underdeveloped countries.

Screening of prostate cancer in Brazil

Very little is known about SPCa in Brazil. Decisions are made mainly based on data collected in other countries with a wide geographic range. A world analysis of PCa incidence by 100.000 inhabitants, according to six groups of countries, showed that USA, Australia and Northern Europe had the highest incidence (83.2 to 173.7), followed by Brazil (45.3 to 83.1). However, these data invert when applied to mortality rates. USA are the fourth group (7.5 to 11.5), but Brazil, Australia and Northern Europe remain in the second place, with 15.3 to 22 deaths by 100.000 inhabitants (12). That means that in North America there is a high incidence of PCa but with low mortality (11). Recently, a Spanish study, where the incidence and mortality are similar to USA, showed no benefit of screening on mortality, justifying the theory that locals with low mortality do not benefit from screening (13). In Sweden and Denmark, with the same mortality rates than Brazil, screening lead to lowering of the rate more recently (2, 3).

It is known that under-notification is a serious problem in Brazil. Officially, the National Institute of Cancer estimated in 2014 that the Southern region of Brazil was more affected, with 91/100.00 inhabitants, followed by the Southeastern (88/100.000), Midwest (63/100.000), Northeastern (47/100.000) and Northern region (30/100.000) (14). Data of Sao Paulo Population Cancer Registry (2000-2005) showed a PCa rate of 337/100.00 in men with 60-64 years old and of 1.137/100.000 in men with 80-84 years (11). Other studies showed rates of 112/100.000 (Brasilia) and 99.3/100.000 (Goiania) (11, 15-19), higher than those published internationally. This wide variation may reflect the differences of health access in our country, low notification and possibly any specific population variation still unknown.

In Brazil, there is no active population screening such as those for breast and uterine cervix cancer. Some men are submitted to exams when spontaneously seek medical attention (16). In 2011, the National Health System of Brazil (SUS) paid 17 million gynecological consultations and only 2.6 million urological consultations (DATASUS). Male population from 45 to 75 years old, the target population for screening, was around 21 million in 2011 and SUS paid 3.9 million PSA exams (total and free). Since many of these exams referred to patients already diagnosed with PCa for follow-up purpose (around 1.7 million patients (17)), many men performed more than one exam/year without medical referral, a significant amount of patients performed the exam privately, and it is possible to infer that less than 15% of that population dose PSA. In Brazil, there are three major health systems: the public one, responsible for 76% of medical care; complementary, including medical insurance companies responsible for 23% of population; and the private system, responsible for 1% (Health Ministry, 2010).

A study involving 135 physicians with ≥51 years old from the Medicine School of the Federal University of Minas Gerais showed that 21% never dosed PSA (15). In Brazil, the reasons for refusal

of PSA dosage and rectal exam include: age <70 years, less than 8 years of schooling, per capita income lower than 0.5 minimum wages (11). Among other countries, these rates are much higher. In the US, around 67% of men ≥60 years old had collected PSA in the last 12 months. In another American study based on the 2000 census, 62% of men ≥65 years old dosed PSA in the last year (11). At Tirol, after PSA became available in public health system, 86.6% of men performed the exam. In Japan, screening is similar to ours, 10% of men perform the test. However, we cannot state that there is or there was SPCa in Brazil.

Prostate cancer is usually more aggressive in lower ages and in blacks/browns, the majority of our population (Brazilian Institute of Geography and Statistics, IBGE 2010: 97 million), different from the USA population. Fortunately, we live in a country with high miscegenation. According to Darcy Ribeiro (20), there is an "in common multi-ethnic genetic background" and it is very difficult to distinguish men according to race. A recent research by the Catholic University of Brasilia showed that 45% of all Brazilians, black and whites, have 90% of African sub-saharan genes and that 86% present up to 10% of African sub-saharan genes, but European ancestry predominates in 80% of individuals (21).

It should also be pointed out some aspects of men from rural zones. Even main global statistics on cancer (Globocan) affirm that they only deal with only 30% of world population. In Brazil, rural population is 16%, or 30.4 million, and there are 15 million of men (IBGE-CENSUS 2010). Besides, men who live in small cities and those marginally to big cities, as well as those from slum dwells, have very little access to medical attention. The timetable of public health services, the decoration with female and childish motives of public campaigns and the need of a second attendance for PSA collection and a third one for physician analysis of the results also contribute for those low number of men screened. At the evaluation of AMS 2009 (Medical Assistance, 2009, IBGE), only 5.2% of public health services without hospitalization had clinical exams available (22).

We should also rethink the strategy to not screen men with less than 10 years of life expectancy. We should rethink life expectancy in Brazil. According to IBGE, life expectancy in Brazilian at birth is 74.6 years; Santa Catarina is the state with higher life expectancy, 76.8 years. In the nineties, when most papers were published about survival of PCa, life expectancy was 66 years, and men died due to other causes not related to low morbidity and mortality of prostatic tumor (DATASUS). Moreover, these are data related to life expectancy at birth. We have to consider that, as long as we survive diseases and accidents, we prolong our life expectancy. According to SUS Health National System table used to guide benefits, that takes into account life expectancy from a determined age, a person with 55 years old would have a life expectancy of more 25.5 years, a person with 65 years more 18 years and with 70 years of more 14.6 years (18). Therefore, it is a mistake to estimate life expectancy of a person over 65-year old, adding inherent risks to a period anterior to his/her time line.

Several aspects must be discussed when we analyze screening above 70 years, such as co-morbidities and choice of treatment, aside from life expectancy. It is important to have in mind the aggressiveness of PCa. In a recent Swedish prospective study showed how low risk tumors treated conservatively presented a considerable risk of progression and death after 15 to 29 years (20/1000 persons/year and 17.9/1000 persons/year) (23).

Does PSA-based screening have benefits?

Although with low rate of mortality, PCA kills many men in the World. In developed countries, median survival from diagnosis in 5 years is 64%, while in under-developed countries is 41%. World mean is 58%, with 258.000 deaths/year (12). Which are the possible benefits?

Mortality reduction

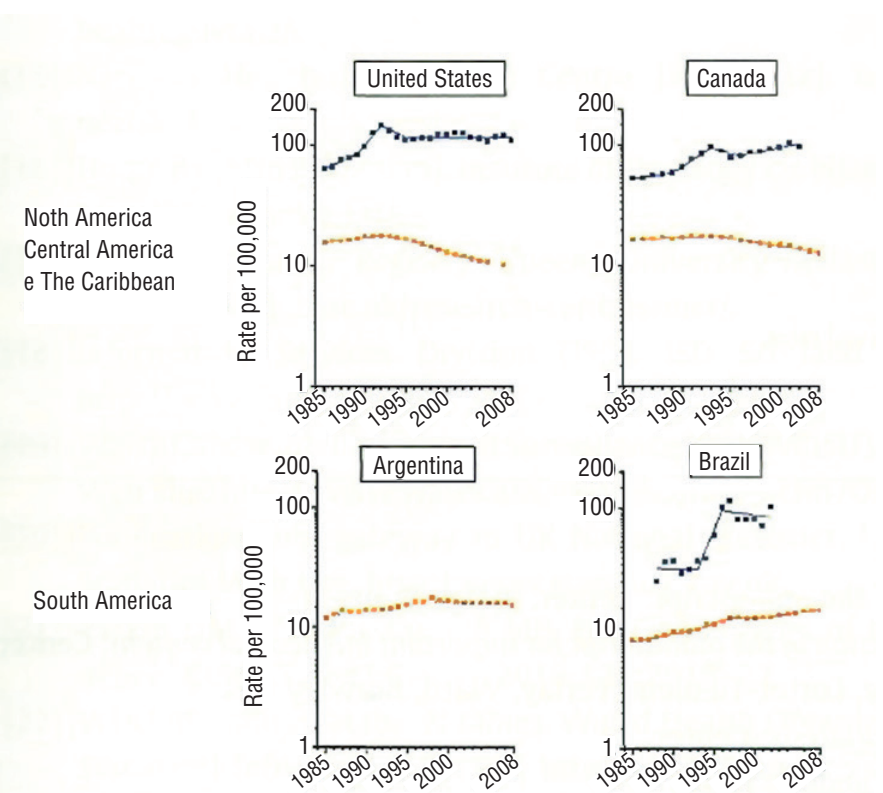
According to the last cancer register in USA, mortality rate lowered 34% from 1990 to 2004 (16). Official data point that reduction after the beginning of PSA based screening and mainly due to PSA-based SPCa and early hormonal treatment derived from the higher number of diagnosis in less advanced stages (SEER - National

Cancer Institute Statistics: http://seer.cancer.gov/csr/1975_2005/). Recently, tendency analysis of incidence and mortality of PCa in the last decades showed distinct figures among countries (Figure-1). While USA and Canada have implemented screening programs and the detection rates raised to a maximum point, reaching a diagnostic plateau, Brazil shows rising detection rates. Moreover, in those countries, the incidence increase of 7% per year of PCa reflects the real increase of incidence of the disease and not the extension of screening programs. And, more important, there was a reduction of mortality in the last decade. In relation to Brazil, mortality rates are still raising, showing that we are lagging behind in relation to screening. When we compare the curves, there is a difference of 20 years.

PLCO, with almost 77.700 participants, in their analysis of anticipation in 7 years of follow-up, showed a death incidence of 2/10.000 persons/year (50 deaths) among screened men versus 1.7 (44 deaths) in control group (9). They concluded that PCa related mortality in screened men is so low that screening is not justified (LE: 1B). A recent Cochrane analysis did not show any reduction on mortality in five randomized studies with a total of 341,342 participants, and stated that there is no reduction of mortality in up to 10 years of follow-up (24). However, these are small studies, with methodologic errors, with level of contamination and, mainly, follow-up inferior to 10 years. It is strange to realize that it was used studies with less than 10 years of follow-up to analyze a disease that does not kill before 10 years after diagnosis.

On the other hand, ERSPC, that included more than 162.000 men with 55 to 69 years old, found, in a follow-up of 11 years, a reduction of mortality of 21%, or 29% after adjustment. But the reduction was significant only for men between

Figure 1 - Incidence tendency and mortality of prostate cancer according to country (Adapted from Center et al. (12))



(blue: incidence; orange: mortality)

65 and 69 years old. They concluded indicating a reduction of 38% of relative risk (RR) in a follow-up of 11 years, but with no reduction for men ≥70 years old (1). An update of the data from Goteborg section with 14 years of follow--up showed a reduction of RR of 50% of mortality in the screened group and 41% reduction of metastasis (2). However, this reduction was accompanied by an important increase of overtreatment. At the initial report of ERSPC, in order to prevent 1 death, they had to screen 1410 men and to treat 48. In the last update, with 11 years of follow-up, it was necessary respectively 1055 and 37. In the Goteborg study of 14 years, it was necessary to screen 293 and to treat only 12 patients in order to avoid one death.

Reduction of cases with metastatic or more advanced disease

Sensitivity and specificity of PSA increase for high grade PCA, showing that it is a better marker for aggressive tumors than for low grade tumors. With screening, there is a higher number of localized disease, lowering the number of metastatic and high grade patients, in the order of 31% (25). Consequently, there is a reduction of pathological fractures, bone pain and the need of treatment, with positive impact on quality of life of those men and families. Prior to PSA era, only 27% of PCa cases diagnosed were localized. In the present, 97 to 98% of all PCas diagnosed through screening are localized (1, 9, 26). Before PSA, 75% of patients died due to cancer or it contributed to death. Mean survival time between diagnosis and death was 41 months (26).

The risk of metastatic PSA reduced 30 and 49% among men screened at ERSPC and Goteborg, respectively. In the last, 2.6% of screened and 10.6% of patients of control group had diagnosis of metastatic disease (2). The absolute risk reduction is of 3.1 cases for every 100 patients screened. Etzioni et al. (27) tried to stablish a reduction of metastatic cases after the introduction of PSA based screening program in a simulated model. With screening, the incidence of metastasis reduced from 77 cases/100.000 men in 1990 to 37 cases in 2000, corresponding to a reduction of 80% of advanced disease (27).

Many studies have shown a reduction of biochemical recurrence following radical prostatectomy in men diagnosed through screening (25) reducing the need of hormone therapy, radiotherapy and chemotherapy and their risks and complications as well as costs of theses auxiliary treatments.

Recently, one study about evolution of metastasis in prostate and breast cancer at diagnosis showed that screening reduced advanced cases of PCa but not of breast cancer. Unlike mammogram, PSA is one of the most efficient markers for high risk diseases, and the reduction of more advanced cases was obtained by screening, and not from reduction of risk factors (Figure-2) (28).

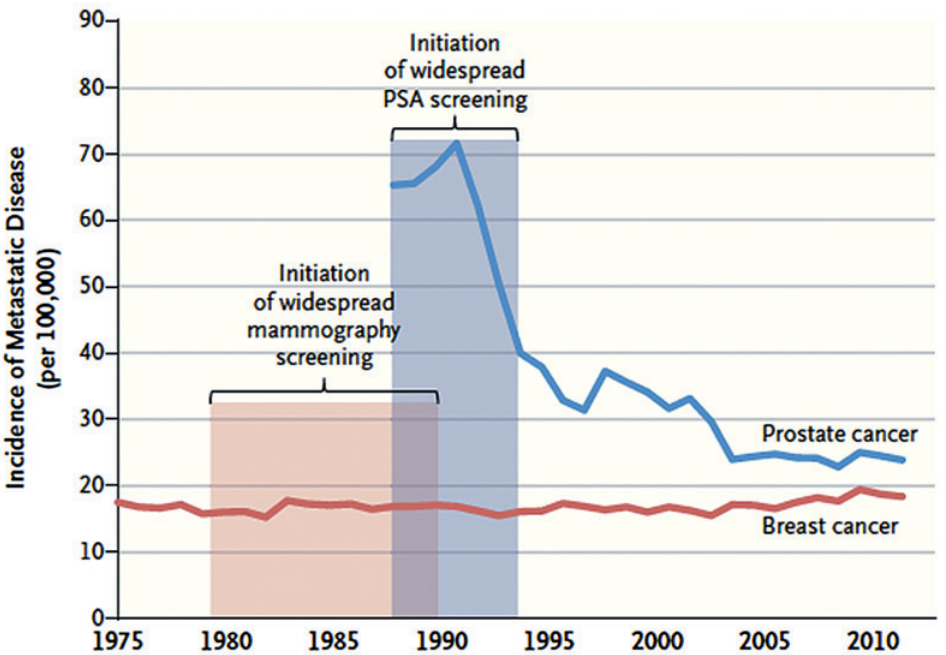
Determination of risk of prostate cancer throughout life

Three key questions are empirical and still not answered: 1) In which age should we start early detection of PCa? 2) In which interval should we perform PSA and rectal exam? And 3) Until which age should we screen for PCa? There are evidences that determination of PSA at 40-45 years is related to future risk of PCa (29, 30). EUA suggests that PSA dosage may be used to define posterior periodicity (LE: B) (31). PSA >1.0ng/mL at 45 years old is associated to a significantly higher risk of death related to PCa, as well as advanced or metastatic disease diagnosis even after 25 years of that dosage (21).

Medium level of PSA of healthy men (Table-1) varies according to age and several studies have shown that a higher PSA of a specific population according to age may be a better indicator for future development of PCa than other clinical risk factors, such as race, familiar history and suspect rectal exam (1, 4, 30, 32).

Västerbotten Intervention Project (33) followed 540 men and showed that among those with basal PSA <0.1ng/mL only 3.9% developed PCA and 1.2% with high risk tumor. Men with PSA from 1 to 2ng/mL have an odds ratio (OR) for PCa of 9.1%, from 2 to 3ng/mL of 23.3 and from 3-4ng/mL of 43.9%. Although that study did not stablish a cut-off level for prediction of PCa, it was able to determine that initial value <1ng/mL

Figure 2 - incidence of metastatic cancer at diagnosis, USA, 1975-2012.



Breast cancer data (SEER) of women ≥40 years old, and prostate cancer (American Joint Committee Stage IV) of men ≥40 years of age (28).

was associated with a very low chance to develop clinical tumor in the future. However, data obtained by the Malmo Preventive Project (30) indicate that screening should be applied in men even with basal PSA below medium, since 28% of metastatic PCa showed levels below medium for up to 27 years.

Even for men over 60 years old, PSA value can predict future risk of PCa, development of metastasis and death at 85 years old. Men in that age group with PSA ≥2ng/mL has 26 more times risk of death due to PCa than those with <2ng/mL (34, 35).

Table 1 - PSA mean level in healthy men (29).

Age	PSA (ng/mL)
30 - 49	0.6 a 0.78
50 - 59	0.7 a 1.23
60 - 64	1.2
65 - 69	1.43

Frequency of screening

Basal PSA, obtained from 45 to 59 years of age, can help urologist/oncologist to plan interval of PSA and rectal digital exams. An evaluation of the Rotterdam section of ERSPC indicates evaluation every 2 to 4 years for men with PSA >1.0ng/mL and of up to 8 years for values <1ng/mL. That study followed 1703 men with 55 to 65 years of age during 8 years with PSA ≤1.0ng/mL and diagnosed only 8 cases of PCa (0.47%) (36). The interval varied in the ERSPC study, and most centers used an interval of 4 years, and the Goteborg arm, 2 years. The interval of 2 years resulted in a reduction of death by PCa RR of up to 44% and of 43% for advanced disease. However, it increased the number of diagnosis of PCa and the incidence of low risk cancer, elevating overtreatment. Although there is still no clear definition of the precise

interval the urologists must individualize it based on basal levels of PSA and on co-morbidities and life expectancy of their clients (1).

Does PSA-based screening have risks?

Diagnosis of low important disease (overdiagnosis)

Some fear that PSA based SPCa could lead to excessive diagnosis, and consequently, overtreatment, with a sequence of unfavorable facts and events and lowering quality of life (5, 37). This is one of the reasons that made USPSTF be unfavorable to SPCa (4). In the last decades, a few steps were introduced in diagnosis and treatment of PCa. Only PCa locally advanced were operated at EDR. After the introduction of PSA, all tumors are treated and diagnosed without distinction, with overdiagnosis and overtreatment. After a sequence of natural learning, many PCa diagnosed by PSA may and must be submitted to active surveillance.

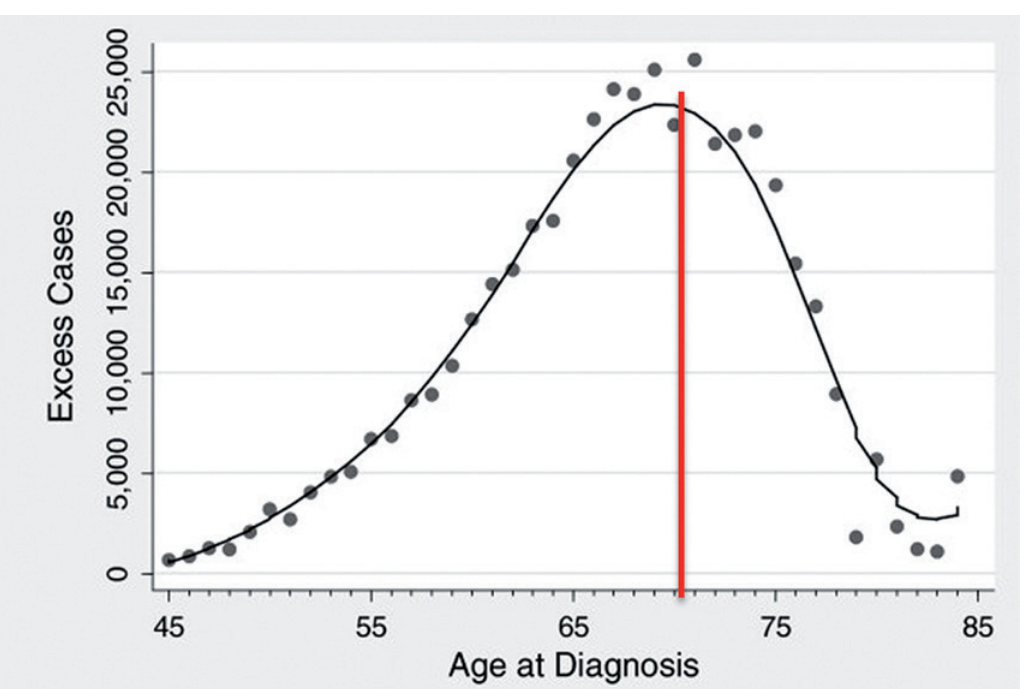
Frequently, the studies report overdiagnosis when analyzing PSA results as a whole, regardless age (38). Almost half unnecessary diagnosis by PSA are made in men older than 70 years, an age group with very few indications of screening (Figure-3). In a simpler way, only controlling that practice would reduce in half overtreatment. Another measure would be to restrict screening in men >60 years old to those with PSA >1ng/mL, informing those with lower age that an eventual PCa diagnosis would rarely cause death.

Recently, data from the Prostate Cancer Intervention Trial (PIVOT) (4) were published. They randomized 731 men to radical prostatectomy (RP) and observation. Some conclusions regarding screening were made. After 10 years, mortality among participants with PSA ≤10ng/mL was 46% with RP vs. 44% for observation (RR 1.06; 95% CI, 0.87-1.29), but for men with basal PSA >0ng/mL it was 48% for RP vs. 62% for observation (RR, 0.79; 95% CI, 0.63-0.99). These data suggest that it could be adopted an increase in the traditional threshold for biopsy indication without prejudice to treatment, avoiding diagnosis with low PSA of a non-clinical significant disease (39).

Adverse effects of screening and treatment

Recent studies have shown a rate of moderate/severe adverse effects in men submitted to

Figure 3 - Number of cases with excessive diagnosis of prostate cancer according to age, from 1987-1995 (47).



biopsy (TURPB) relatively low, such as hemospermia (27%), pain (75), hematuria (6%), fever (6%), hematoquezia (2%), and risk of hospitalization of 0.5-1.3% (40, 41). However, population studies show that this hospitalization rate can reach 7% (42). Per-operatory mortality of PC is around 0.5% and absolute risk of urinary incontinence is 11%, and erectile dysfunction 43%. In the long term follow-up, surgical and radiotherapy complications are similar (39).

Difficulties of the background studies

Follow-up time

As referred above, grade D recommendation of AUA and of United States Preventive Services Task Force (USPSTF) (43) was based mainly in two studies, with conflicting results (Table-2). ERSPC study had a great number of participants with an adequate follow-up and PLCO had half participants and partial publication of data (44, 45). Both studies had short duration. It is believed that any alteration of the natural slow history of PCa should occur only after 11.5 years (46). One of the long arms of ERSPC (Goteborg Trial) with 14 years of follow-up showed reduction of 44% of mortality among screened men. The great paradox is that AUA's SPCa guidelines for more than a decade indicate that we must not screen men with life expectancy ≤10 years, but when it evaluated SPCa benefits they based on studies with shorter follow-up. We must remember that those studies were planned 20 years ago, when the knowledge of natural history of PCa was a fraction of what is known nowadays.

Since most deaths occur in men over 70 years old (47) and both studies included men >50 years, ideal follow-up time to determine reduction of mortality should be longer than 14 years, since many participants did not reach the group age when death occurs.

Tumor data

PLCO did not find advantages with screening and involved a smaller number of patients with more advanced disease and with Gleason score lower than ERSPC (1, 9). With a larger number of PCa with low or intermediate risk, the tendency is low mortality. It is known that for these groups screening is not essential. This "aggressiveness shift" may be revealed by the published low mortality (<0.3%). There were 174 tumor-specific deaths at PLCO. That fact was observed since almost half participants had at least two previous PSA exams, and those with PCa diagnosis were not included in neither study arms, being pre-selected.

Power of the study

We must remember that at analysis of strength of PLCO, 37.000 men should be initially

Table 2 - Comparison of two major studies of prostate cancer screening.

Item	ERSPC (Schroder et al.) (1)	PLCO (Andriole et al. (9)
Sample	182,000 men 50 to 74 years old	76,693 men
Local	European countries	10 North-American center
Biopsy	PSA > 3ng/mL	PSA > 4ng/mL
Follow-up	9 years	7 years, with 10 years with only 67% of data
% biopsy	85.8%	40.2% (7 years) and 30% (10 years)
Stage	Most PCas in both arms were stage I	Most PCas in both arms were stage II
Gleason	Most in both arms were Gleason 2 to 6 (at biopsy)	Most in both arms were Gleason 5 and 6 (at biopsy)
Mortality	Reduction of 20% in the screened group, 31% in the arm really screened. Goteborg arm with 14 years and 44%	Low mortality in both arms, without difference

(Adapted from Bailey et al. (44) and Schoder et al. (45)).

evaluated in each arm during 10 years. However, only 67% of mortality data were available in that period. Besides, changes after the beginning of the protocol in 1995, such as reduction of access age to 55 years, resulted in reduction to accuracy and new calculations in order to maintain accuracy, with the need of follow-up of more 13 years from the last modification, that occurred in 2011. Only these two aspects, according to statistics, reduce the power of the study in 50% (48).

Study contamination

One of the methodological bias of PLPO was that almost half candidates admitted in the group control of the study had already performed occasional PSA dosages. This situation is common in regions where screening has already been implemented. This previous evaluation works as a "pre-selection" and a selection bias, since many PCas had already been identified, and therefore, were left aside from the study. One proof is the presence of lower number of patients with advanced PCa and/or high Gleason score (≥7) than other publications (4).

It is accepted a maximum of 20% of contamination, but at PLCO almost half participants had performed a previous PSA exam. Therefore, under an epidemiologic point of view, we can affirm that PLCO compares two kinds of screening: more and less intense (9).

What will happen if we stop screening?

If we suspend screening (Brazil never had screening) indiscriminately we will eliminate the risks but also the benefits (49). One of the reasons for the reduction of morbi-mortality of PCa of PSA-based screening was downstaging (36) at diagnosis. If we stop screening favorable effects will no longer persist (5). However, since 93% of deaths due to PCa occur in men >70 years old (50), period in in which a more number of high grade of PCa are diagnosed, the suspension of screening in men <65 years will increase morbi-mortality in that age group in a few years (51).

Bergdahl et al. (51) followed 13.423 men: half of them stopped screening at 69 years of age and half (control group) never were screened. In the first 9 years of the last PSA all risk groups of PSA were more frequently diagnosed among those never screened, but after 9 years, the rates were the same, except for groups with low risk. The reduction of advanced and high risk PCa observed in the screened arm during the screening period lasted for 9 years. After that period, mortality rate of those screened reached that of the group never screened (51). Therefore, after 9 years, the welcome displacement of stage to less advanced disease and with lower risk was lost. Also interesting, the authors noted a gradual drop of the protective effect of screening, starting after 4 years of the last PSA. The authors informed that, as a consequence of suspending screening at 69 years of age, men ≥78 years will have the same risk of advanced of high risk disease than those not screened.

Rational use of PSA

If the specialists do not agree if we should or not perform screening, we cannot expect patients to decide for that measure with less information. AUA guidelines suggest that we should screen patients who understand and accept the risks. However, this approach could result in different health care management, since well-educated and informed men would ask for screening and would be effective screened (37). And certainly that recommendation would not be applied to the majority of the Brazilian population, in view of the disparity of socio-economic status of our population than that of USA.

More recent data indicate that the real discussion is not if we should perform PSA based screening of PCa but how to do it rationally. Most authors agree that annual screening of all men ≥50 years old is not justified (26, 44, 52-54). Screening programs must focus on the decision capacity of PCa experts (urologists and oncologist) and not on basic health programs. Table-3 shows some guidelines that help perform a more smart screening.

CONFLICT OF INTEREST

None declared.

Table 3 - General measures that may help define guidelines for prostate cancer screening.

1. PSA dosed at 45-50 years old may identify risk groups and indicate screening interval
2. Reduce intensity of screening > 60 years old in men with PSA<2.0 ng/mL
3. There is little benefit to screen men>70 years old, with PSA≤3.0 ng/mL and with two or more co-morbidities
4. Smart screening in men 50-69 years old
5. Screening intervals from 2/2 years up to 7/7 years, individualized
6. Attention to familial prostate cancer, defined as two first-degree relatives or on first-degree relative and at least two of second-degree
7. Attention to screening in morbid obeses and blacks with good health
8. Population screening for all men is not justified
9. Urologist/oncologist must individualize need and method of screening
10. Consider active surveillance/observation for patients with low risk PCa

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REVIEW ARTICLE

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Prostate cancer in Brazil and Latin America: epidemiology and screening

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ABSTRACT

Introduction: Prostate cancer is one of the tumors with higher incidence and mortality among men in the World. Epidemiological data are influenced by life expectancy of population, available diagnostic methods, correct collection of data and quality of health services. Screening of the disease is not standardized around the World. Up till now there is no consensus about the risks versus benefits of early detection. There are still missing data about this pathology in Latin America.
Objective: to revise current epidemiologic situation and early diagnosis policies of prostate cancer in Brazil and Latin America.
Materials and Methods: Medline, Cochrane Library and SciELO databases were reviewed on the subject of epidemiology and screening of prostate cancer. Screening research was performed in websites on national public health organizations and Latin America. Screening recommendations were obtained from those governmental organizations and from Latin American urological societies and compared to the most prominent regulatory agencies and societies of specialists and generalists from around the World.
Results: Brazil and Latin America have a special position in relation to incidence and mortality of prostate cancer. In Brazil, it occupies the first position regarding incidence of cancer in men and the second cause of mortality. Central America has the highest rate of mortality of the continent with lower incidence/mortality ratios. Screening recommendations are very distinct, mainly among regulatory organs and urological societies.
Conclusion: prostate cancer epidemiology is an important health public topic. Data collection related to incidence and mortality is still precarious, especially in less developed countries. It is necessary to follow-up long term screening studies results in order to conclude its benefits.

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Keywords:
Prostatic Neoplasms; Epidemiology; Early Diagnosis; Latin America

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INTRODUCTION

Prostate cancer is the most prevalent tumor in men, if we exclude non-melanoma skin cancers. According to GLOBOCAN data, one million and a hundred thousand men were diagnosed in 2012, corresponding to 15% of the cancers diagnosed in men (1). The incidence is quite variable around the World and influenced by life expectancy and diagnostic methods applied in each specific geographic region, as well as according to organization of epidemiological data. This is why we observe high incidence in developed regions.

In the same year of 2012, 307.000 deaths due to prostate cancer were estimated around the World, being the fifth cause of death among men

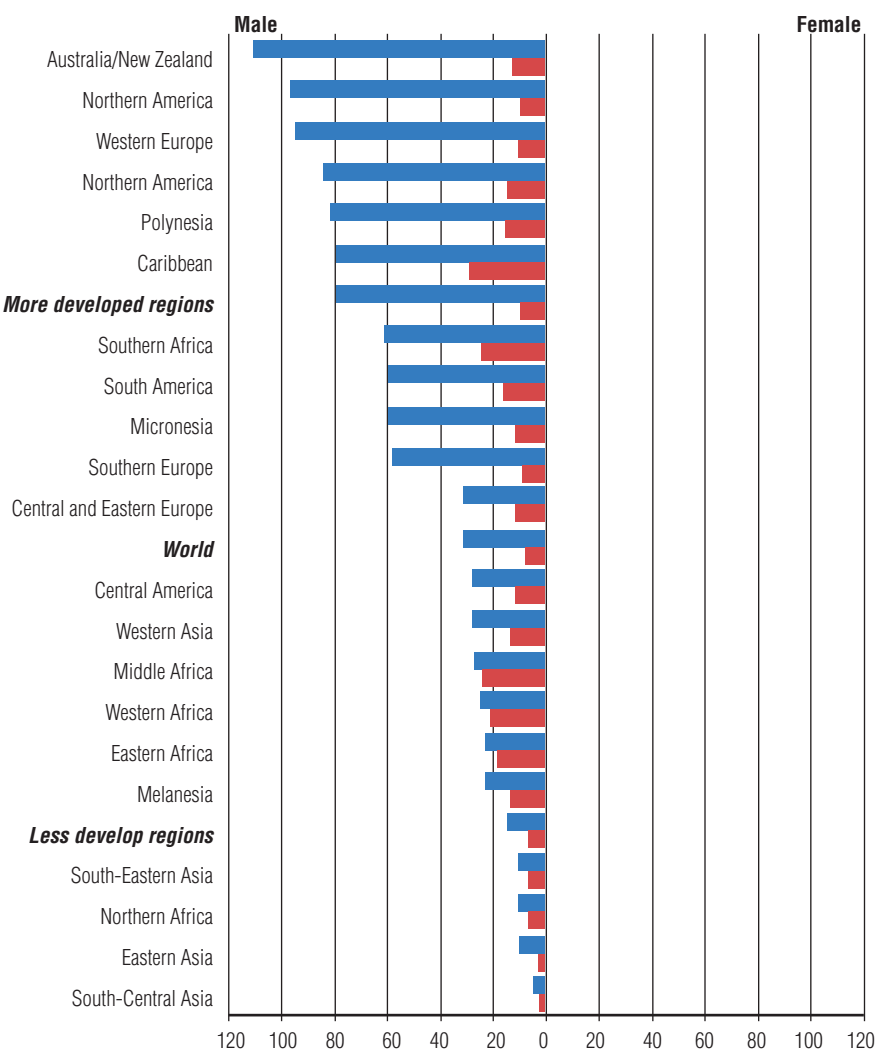
(1). Mortality per region, influenced by the quality of available health services to population, is high among less developed countries. In that matter, it is observed higher incidence/mortality rates in more developed regions (Figure-1).

Early detection of prostate cancer is controversial and not standardized around the World. PSA (prostatic specific antigen) dosage is the most frequent screening method, with better cost/benefit ratio, although with limited specificity. The use of rectal exam, as part of physical exams, is influenced by culture factors among different populations.

Screening is a secondary prevention action for the detection of the disease in earlier stages. Screening programs may be population-based or opportunistic (when a patient seeks medical attention due to other reasons and the physician takes the opportunity to perform the screening).

The purpose of the screening is to detect precociously prostate cancer, to treat it in earlier phases and finally to reduce mortality. PSA false--positive results may present bad consequences to screening , including unnecessary biopsies and their complications (bleeding, infection, hospitalization) and damages due to treatment of con-

Figure 1 - Incidence and mortality rates in World per 100.000 inhabitants Source: GLOBOCAN, 2012.



ditions that probably would not clinically evolve (overdiagnosis and overtreatment). Overtreatment is been handled with observation strategies in very low risk diseases (active surveillance).

The results of two international randomized studies (2, 3) and their updates on the impact of screening on mortality of prostate cancer have been used to guide government health agencies, specialty societies and general medical organizations (4). Those studies were not able to demonstrate reduction of mortality after 10 years of follow-up. However, their updates show that a longer follow-up time has a tendency to treat lower number of patients in order to prevent death. Another aspect is "stage downgrade" after the implementation of early screening policies, with lower PSA, lower number of locally advanced tumors and long distant metastasis (5). In that matter, there has been great divergence among screening recommendations of government organs and medical societies.

Majority of epidemiological data and screening policies regarding prostate cancer are from studies of North America and Europe. Brazil has well defined government, non-government and medical societies policies, and in Latin America, in general, they are scarce.

OBJECTIVE

The purpose of the present study is to review the current epidemiologic situation and health policies on early detection of prostate cancer in Brazil and Latin America, in relation to the World.

MATERIALS AND METHODS

It was performed a search on the databases Medline, Cochrane Library and SciELO on the topics: "prostate cancer", "epidemiology" "early diagnosis", "screening" and their combinations, including papers in all languages. Only studies regarding Brazil and Latin America were included.

Epidemiologic research was performed in the following websites of government agencies: World Health Organization (WHO); Pan-American Health Organization (PAHO), Instituto Nacional do Cancer (INCA-Brazilian Institute of Cancer) and government health department of main countries of Latin America.

It was collected information on prostate cancer screening recommendations, and also from the following medical societies: Brazilian Society of Urology, Argentine Societies (inter-societies Consensum), Sociedad Colombiana de Urología (Colombian Urological Society), Sociedad Peruana de Urología (Peruvian Urological Society) and Sociedad Mexicana de Urología (Mexican Society of Urology).

Latin American recommendations were compared worldwide to those of government and medical societies: U. S. Preventive Service Task Force (USPSTF) - USA, National Health Service (NHS) – United Kingdom, Canadian Task Force on Preventive Health Care (CTFPHC) – Canada; American medical societies: American College of Physician (ACP), American Academy of Family Physician (AAFP); and specialties societies (American and European): American Cancer Society (ACS), American Urological Association (AUA), European Association of Urology (EAU).

RESULTS

Epidemiology

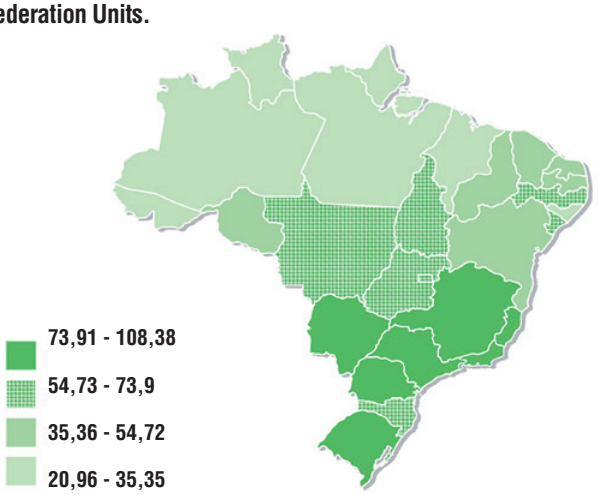
Prostate cancer is the main cancer in Brazilian men, excluding non-melanoma skin cancer. In 2012, there were 60.180 new cases, corresponding to 62 new cases/100.000 men. The most developed regions of the country registered the highest number of cases: 78 new cases/100.000 men in Southeast [40] (Figure-2). The increasing incidence of prostate cancer has been correlated to the increasing life expectancy of Brazilian population, to better assessment of medical data, to higher availability of diagnostic methods and overdiagnosis due to screening policies. There are conflicting data regarding prevalence per race: some studies show higher prevalence in African-american population and others don't demonstrate significant difference (6, 7).

In relation to mortality due to cancer in Brazilian men, prostate cancer is the second main cause of death, following lung cancer (8). In 2012, there were 13.354 deaths due to prostate tumor in Brazil, corresponding to 13% of all deaths due

to cancer in men. Among these, 88% occurred in men over 65 years old (4). Figure-3 presents the distribution of prostate cancer mortality according to Brazilian regions in 2012.

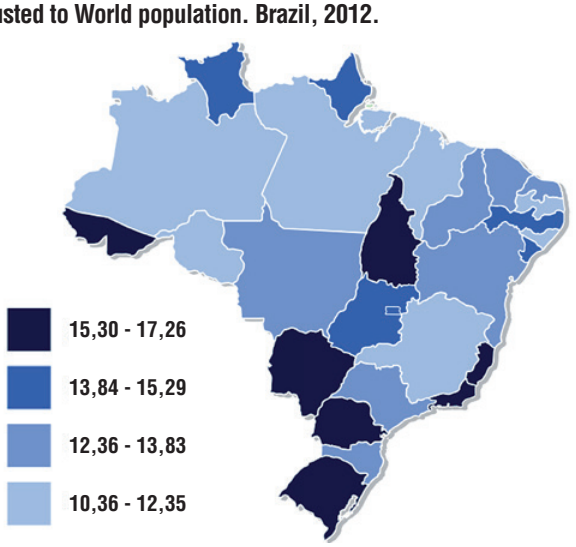
Between 2004 and 2007, Hospital do Cancer in Barretos, São Paulo, Brazil, performed a huge program of prostate cancer screening in 231 Brazilian cities. Seventeen thousand patients over 45 years old were screened by plasma PSA and rectal exam. Among these, only 29% have been previously screened for prostate cancer. Biopsy was indicated in 16.1% of evaluated patients (9). Cumulative rate of prostate cancer detection was 3.7%, similar to what was published regarding North American and European populations (2, 3, 9).

Figure 2 – Crude rates of incidence of prostate cancer, per 100.000 men, estimated for the year 2014, according to Federation Units.



Source: INCA. Estimate 2014: Cancer incidence in Brazil

Figure 3 – Mortality rates of prostate cancer, per 100.000 men, adjusted to World population. Brazil, 2012.



Source: INCA. Atlas of cancer mortality

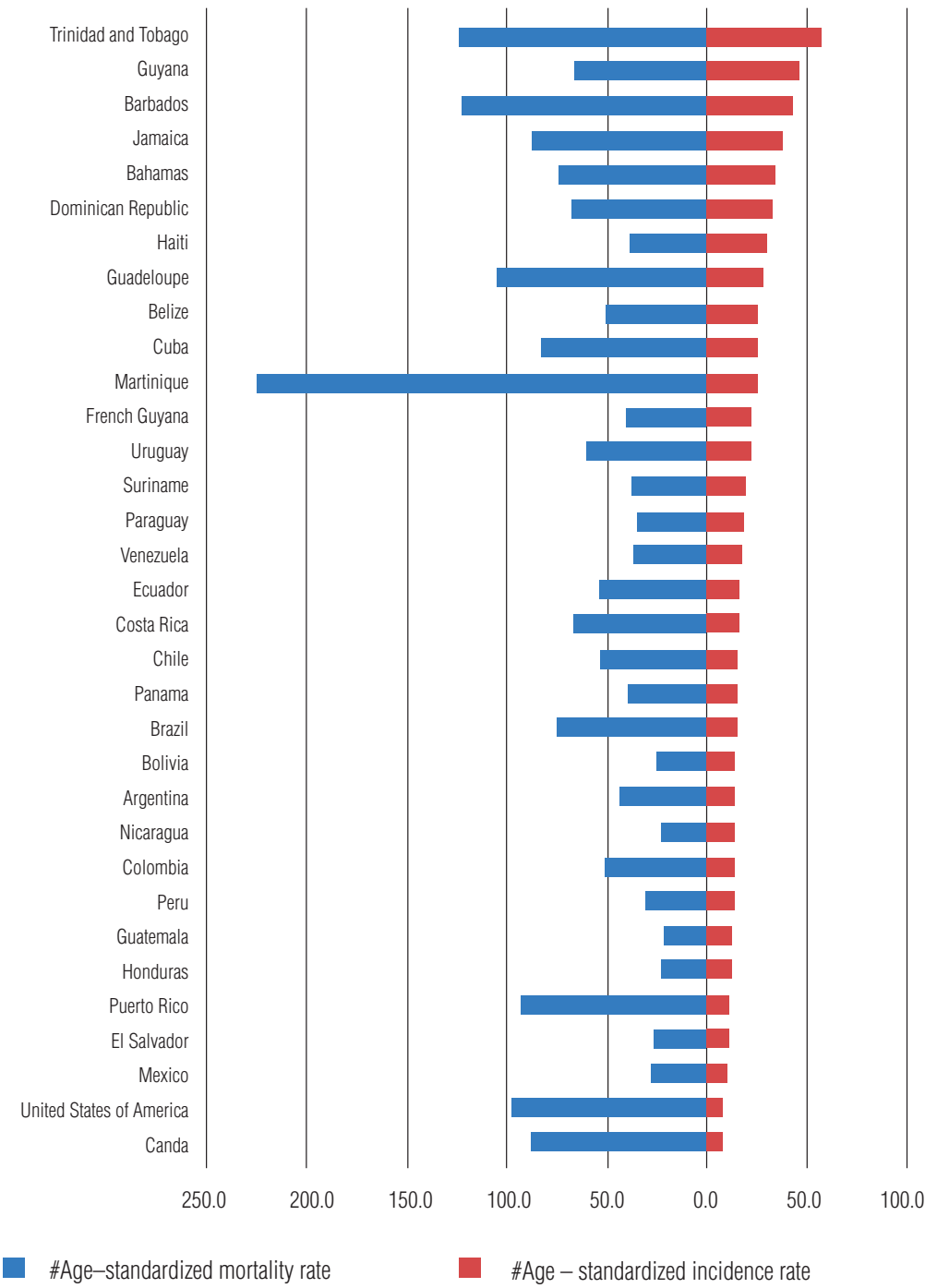
The Brazilian Society of Urology published in 2012 (Nardi et al., 2012) the profile of patients assisted by public and private institutions in Brazil (10). Around 54% of prostate cancer patients were treated in public institutions, including older men (69 years x 67 years, p<0.001), more African-americans (18.3 vs. 7%, p<0.001), with more advanced disease, higher medium PSA value (10.0 vs. 6.8, p<0.001) and higher incidence of metastatic disease (10.4% vs. 4.3%, p<0.001). Among these patients, less than 50% had been submitted to radical prostatectomy, and a high proportion of patients were using hormonal ablation (chemical or surgical) combined or not to radiotherapy.

In a study performed by the Cooperative Brazilian Uro-Oncology Group (CBUG), Tobias-Machado et al. evaluated the association of level of education (schooling), screening and aggressiveness of prostate cancer in Brazil (11). Among illiterate patients, there was a lower rate of screening, and following positive screening, a lower rate of follow-up until definite diagnosis. These patients also showed higher levels of PSA, more advanced stages of the disease and higher Gleason score at biopsies.

According to data of PAHO in 2013, more than 400.000 new cases are detected per year in Latin America, with higher incidence in Central America (8) (Figure-4). It is observed an increasing incidence in Latin America, and it is expected to double by the year 2030 (Figure-5). In more developed countries, such as USA and Canada, although there is a high incidence related to early diagnosis and high quality of information systems, their mortality rates are the lowest in the continent, with high incidence/mortality rate.

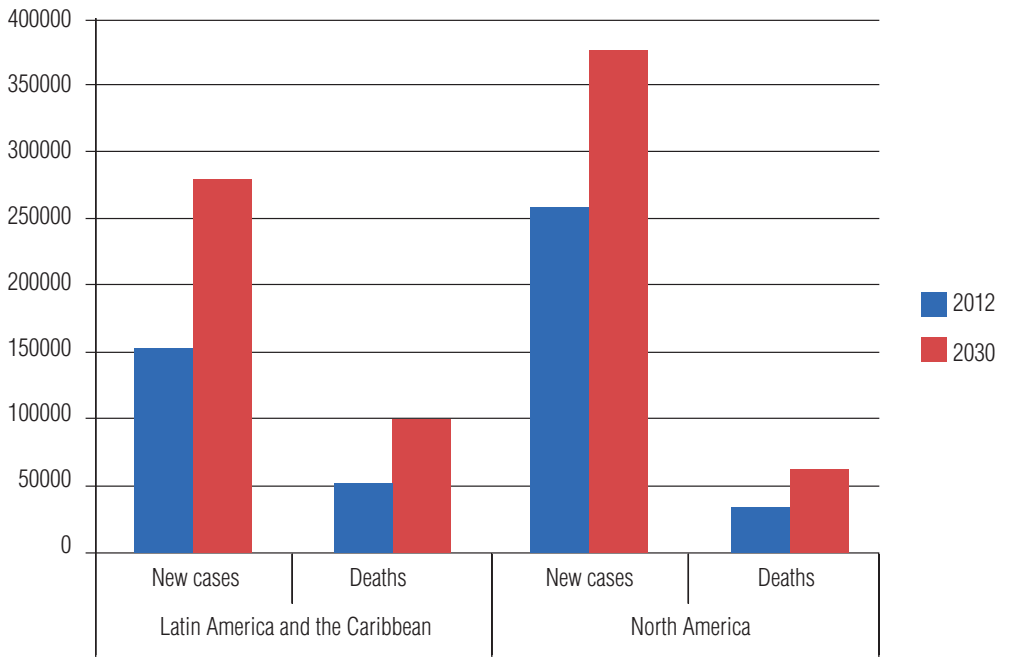
Mortality in America is still high, with 80.000 new cases per year, being the second most frequent cause of death due to cancer in men (8). These numbers are higher in Central America, followed by South and North America. There are

Figure 4 – Incidence and mortality rates of prostate cancer in each American country, 2012.



Source: GLOBOCAN, 2012

Figure 5 –Estimate of new cases and deaths due to prostate cancer in 2012 and 2030, in the Americas.



Source: GLOBOCAN, 2012

higher rates of incidence/mortality in countries more developed and with higher Gross National Product (Figure-6).

Individual epidemiological data of different countries are scarce and few present organized and accessible data, such as Argentina and Colombia. High incidence and mortality are common in all, and prostate cancer is the second cause of death in both. Around 4.000 deaths due to prostate cancer are registered in Argentine per year and more than 2.500 in Colombia (12, 13). Mortality tendency between countries is different, as well as the health approach regarding diagnosis and treatment. In Argentine, there is a tendency to lower mortality due to better treatment in the last years (14). On the other hand, Colombia presented a recent increase in mortality (1.7% per year), related to higher diagnosis rates and better information of data (13).

Screening

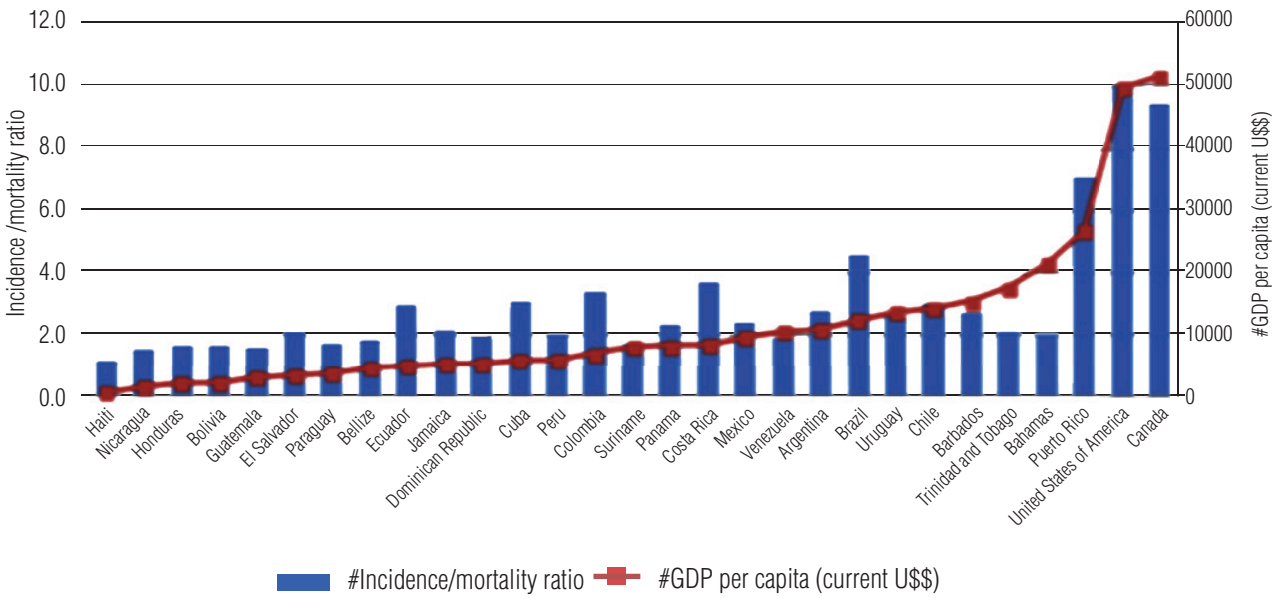
Screening recommendations for early detection of prostate cancer are divergent around the World, especially among government agencies and medical societies (Tables 1 and 2).

Internationally, health organizations of North America, Canada and United Kingdom are against population screening. For example, in United Kingdom, there is no screening program for prostate cancer based on PSA, according to recommendations of NHS of 2015 (15). Also, the regulatory agencies of the two biggest countries of North America, USPSTF (2012) and CTFPHC (2014) are contrary to organized population screening (16, 17).

INCA, an organ from the Health Ministry of Brazil, in 2013, also is contrary to population screening, since their risks overpass the benefits. However, in cases of spontaneous demand, the agency recommends to orientate the patient about the risks versus benefits and shared decision (18).

Accordingly, Ministerio de Salud and Instituto Nacional del Cancer of Argentine do not recommend population screening (12). In Mexico, the Secretaria de Salud (Health Secretary) is one of the few government agencies to recommend PSA

Figure 6 – Incidence/mortality ratio of prostate cancer, compared to GNP per capita per country, 2012.



Source: GLOBOCAN, 2012

Table 1 – Prostate cancer screening recommendations of regulatory government agencies.

Regulatory agencies	Screening recommendations
NHS (2015) - United Kingdom	Not recommended
USPSTF (2012) - USA	Not recommended
CTFPHC (2014) - Canada	Not recommended
INCA/Health Ministry (2013) - Brazil	Organized population screening not recommended. If spontaneous demmand, inform risksxbenefits
INC/Ministerio de Salud de la Nación - Argentina	Not recommended
Secretaria de Salud - México (2010)	Patients >5y or >40a + risk factors
Ministerio de Salud e Protección Social – Colombia (2013)*	Organized population screening not recommended. Early opportunity detection if >50y or <50y + risk factors. Frequency ≥5 years.

*Ministerio de Salud and Sociedad de Urologia de Colombia recommendation
NHS = National Health Service; **USPSTF** = U. S. Preventive Service Task Force; **CTFPHC** = Canadian Task Force on Preventive Health Care; **INCA** = Instituto Nacional do Câncer (Brasil); **INC** = Instituto Nacional del Cancer (Argentina)

and rectal exam to patients with more than 50 years old or above 40 years with risk factors (19).

Among general medical societies, AAFP (2013) follows the recommendations of government agencies, against screening, independent of age (20). Meanwhile, ACP (2013) orients to not offer early detection for patients under 50 years old, above 70 years or with life expectancy lower than 15 years, but recommends shared decision for patients between 50 and 59 years old (21).

Specialties societies present different visions of government agencies: they widely recom-

Table 2 – Recommendations of prostate cancer screening of specialty societies.

Specialty society	Screening recommendations
American Urological Association - AUA (2013)	<40y or >70r or <10-15r de LE: do not screen 40-54y: offer screening if with high risk[1] 55-69y: offer screening
European Association of Urology - EAU (2015)	Men>50 years old Men>45 year + familial history African-Americans PSA>1ng/mL at 40 years old PSA>2ng/mL at 60 years old
American Cancer Society - ACS (2015)	>50 years + LE >10 yeqrs >45 years + high risk[1] >40 years + very high risk[2]
Sociedade Brasileira de Urologia - SBU (2013)	>50 years >45 years + high risk[1]
Consenso Nacional Inter - Sociedades (2014) – Argentina	<40y or >70y + comorbidities: do not screen 40-55y: if with high risk 55-70y or >70y without comorbidities: shared decision
Sociedad Colombiana de Urologia (2013)*	Organized population screening not recommended Early opportunity detection if>50u or <50y + risk factors Frequency ≥5 years.
Sociedad Peruana de Urología	>50 years >40 years + high risk[1]
Sociedad Mexicana de Urologia	>45 years

* Ministerio de Salud and Sociedad de Urologia de Colombia recommendations
LE = Life expectancy
[1] High risk: 01 first-degree relative with prostate cancer or African-american
[2] Very high risk: >01 first-degree relative with prostate cancer

mend screening with tiny differences regarding the candidate patients and interval. Among international societies, AUA (2013) recommends screening patients between 55 and 69 years old, and above 40 years for patients with high risk (22). ACS (2015), an oncological society, suggests discuss screening for patients with more than 50 years old, and life expectancy over 10 years or above 45 years in the presence of high risk factors (African-americans or first-degree relatives with prostate cancer) or above 40 years if with high risk (more than a first-degree relative with prostate cancer) (23). EAU (2015) also recommends screening for patients over 50 years old or with more than 45 years with risk factors; they also recommend to screen men over 40 years old with PSA higher than 1ng/mL or older than 60 years with PSA higher than 2ng/mL (24).

In Brazil, SBU strictly recommends population screening and it pioneered men education regarding the issue. In 1996, the society started educational campaigns with artists, encouraging men to screening. In 2012, the campaign "Campanha Novembro Azul" was proposed in order to stimulate men over 40 years old to seek preventive exams. In the last update of 2013, SBU claims that the target population are men over 50 years old or above 45 years if with high risk (African-americans, or with familial history of first-degree relatives) (25).

Latin American societies, as in Brazil, recommend screening with PSA dosage and rectal exam.

Peruvian society recommends screening for men over 50 years old or above 40 if with high risk (26). In Mexico, the urological society recommends screening for men over 45 years old (27). National Consensum of Argentinian Inter-societies follow AUA recommendations (28). In Colombia, the Ministerio de Salud e Protección Social and Sociedad Colombiana de Urologia (Guia de Práctica Clinica, 2013), do not recommend organized population screening, but early detection by opportunity for men over 50 years old or below 50 years if with risk factors. Contrary to others, the screening interval should not be inferior to 5 years (13).

CONCLUSIONS

Prostate cancer epidemiology by itself reinforces the impact of that disease in public health. The World is facing the disease with attitudes to lower the associated morbidity and mortality. Brazil is ameliorating the combat to that disease, adopting policies of early detection, improvement of diagnosis and treatment, but most Latin American countries do not follow this advances, also with lack of correct information. The result is the observation of high rates of mortality, mainly in Central America.

Screening policies are divergent among countries and even internally, among government agencies and medical societies. Long follow-up of large international studies will establish the importance of screening and will help define future recommendations. However, the frequent demands for implementation of screening programs must be followed by correct actions of diagnostic confirmation and treatment.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Oncological outcomes following radical prostatectomy for patients with pT4 prostate cancer

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ABSTRACT

Objectives: Radical prostatectomy (RP) for locally advanced prostate cancer may reduce the risk of metastasis and cancer-specific death. Herein, we evaluated the outcomes for patients with pT4 disease treated with RP.
Materials and methods: Among 19,800 men treated with RP at Mayo Clinic from 1987 to 2010, 87 were found to have pT4 tumors. Biochemical recurrence (BCR)-free survival, systemic progression (SP) free survival and overall survival (OS) were estimated using the Kaplan-Meier method and compared with the log-rank test. Cox proportional hazards regression models were used to assess the association of clinic-pathological features with outcome.
Results: Median follow-up was 9.8 years (IQR 3.6, 13.4). Of the 87 patients, 50 (57.5%) were diagnosed with BCR, 30 (34.5%) developed SP, and 38 (43.7%) died, with 11 (12.6%) dying of prostate cancer. Adjuvant androgen deprivation therapy was administered to 77 men, while 32 received adjuvant external beam radiation therapy. Ten-year BCR-free survival, SP-free survival, and OS was 37%, 64%, and 70% respectively. On multivariate analysis, the presence of positive lymph nodes was marginally significantly associated with patients' risk of BCR (HR: 1.94; p=0.05), while both positive lymph nodes (HR 2.96; p=0.02) and high pathologic Gleason score (HR 1.95; p=0.03) were associated with SP.
Conclusions: Patients with pT4 disease may experience long-term survival following RP, and as such, when technically feasible, surgical resection should be considered in the multimodal treatment approach to these men.

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INTRODUCTION

In 2016 there will be approximately 180,890 new cases of prostate cancer and 26.120 related deaths in the US (1). Despite the noted stage migration in prostate cancer over the course of the PSA era, approximately 10% of patients present with locally advanced disease, which increases the risk of disease progression and mortality after initial treatment (2). Historically, the majority of patients with high-risk prostate cancer have been managed with external beam radiation therapy (EBRT) and androgen deprivation therapy (ADT) (3-6).

More recently, several observational series have demonstrated the technical feasibility of

radical prostatectomy (RP) in the setting of high-risk disease and have reported 5-year progression-free survival rates of approximately 85% (7-10). While in high-risk disease, surgery is often a component of a multimodal treatment approach; RP provides accurate pathologic staging of both the primary tumor and pelvic lymph nodes and may afford durable local control. Of note, the majority of surgical series on locally advanced disease have consisted of patients with either clinical or pathologic T3 tumors. Indeed, the treatment outcomes and prognostic variables for patients with pT4 prostate cancer remain poorly described. Here, we evaluated our experience with RP for patients in whom the final pathologic analysis demonstrated pT4 disease. Specifically, we analyzed the long-term rates of biochemical recurrence (BCR), systemic progression (SP) and overall survival (OS) following surgery as part of a multimodal treatment approach. Furthermore, we identified clinico-pathologic variables associated with oncological outcome in these men.

MATERIALS AND METHODS

Patient selection

After Institutional Review Board approval (#12-007416) was obtained, we reviewed our Prostatectomy Registry and identified 19,800 patients who underwent RP between 1987 and 2010. Surgical procedures were performed using standard techniques. For the uniformity of diagnosis and staging, all the cases were reviewed by central pathology laboratory and surgical specimens were processed according to standard pathological procedures and staged according to the 2009 American Joint Committee on Cancer staging system for prostate cancer (11). A total of 87 men were found to have pT4 disease, and form the study cohort here. Out of these, 7 patients underwent robotic radical prostatectomy with pelvic lymph node dissection (PLND) and 80 underwent radical retropubic prostatectomy with PLND. Pelvic lymph node dissection was performed utilizing the following template-we completely removed all lymph node tissue along the external iliac vein, the distal limit being the deep circumflex vein and the femoral canal. We removed all fibrofatty tissue from the obturator fossa to completely skeletonize the obturator nerve. Proximally, PLND was performed up to and including the bifurcation of the common iliac artery. The lateral limit consisted of the pelvic sidewall, and the medial dissection limit was defined by perivesical fat. In high-risk patients included in our cohort, LNs along the internal iliac vessels were dissected.

The retrospective nature of our dataset precludes a standardized approach to surveillance; however, postoperative assessments, including physical examination and serum PSA measurement, were generally done quarterly for the initial 2 years after surgery, semi-annually for an additional 2 years, and annually thereafter. Adjuvant therapy was defined as treatment received ≤90 days of RP, and was given at the discretion of the treating physician, while salvage therapy was defined as treatment received >90 days after RP, and was likewise administered based on clinician's discretion. BCR was defined as a PSA level of ≥0.4ng/mL (12). SP was defined as demonstrable metastasis on radionuclide bone scan or on biopsies outside the prostatic bed. Vital status was identified from death certificates or physician correspondence. For patients followed elsewhere, the Mayo Clinic Prostatectomy Registry prospectively monitors outcomes annually by correspondence.

Statistical analysis

Continuous features were summarized with medians and interquartile ranges (IQR); categorical features were summarized with frequency counts and percentages. The Kaplan-Meier method was utilized to estimate BCR-free survival, SP-free survival and OS, with differences assessed with log-rank test. Patients were censored at last follow-up or death if the endpoint of interest had not been attained. Cox proportional hazards model was used to estimate the association of clinic-pathologic variables with patient's risk of BCR, SP, and all-cause mortality. Statistical analysis was done using SAS®, version 9.2. All tests were two-sided, with $p \leq 0.05$ considered to indicate statistical significance.

RESULTS

Of 19,800 patients who underwent RP during the time period of study, we identified 87 (0.43%) patients with pT4 disease. Median age at surgery in these men was 65 years (IQR 58, 69). Median preoperative PSA was 12.2ng/mL (IQR5.7, 34.9). Table-1 lists the clinic-pathological features for this cohort. Moreover, 30 (34.5%) and 4 (4.6%) patients received androgen deprivation therapy (ADT) and external beam radiation therapy (EBRT), respectively, prior to RP.

Median follow-up after RP was 9.8 years (IQR 3.6, 13.4), during which time 50 patients experienced BCR, 10 were diagnosed with a local recurrence, 30 developed SP and 38 died, with 11 dying of prostate cancer. A total of 77 men were treated with adjuvant ADT, while 32 received adjuvant EBRT. We noted that the 10-year BCR-free survival in these patients was 37%, while 64% were free from SP and the overall survival was 70% (Figure-1).

Table 1 - Clinical and pathological features of pT4 prostate cancer patients.

	Total (n=87)
Clinical T Stage	(n=85)
T1c	15(17.6%)
T2a	20(23.5%)
T2b	11(12.9%)
T3/4	39(45.9%)
Biopsy Gleason Score	(n=54)
≤6	13(24.1%)
7	14(25.9%)
8-10	27(50.0%)
Pathological Gleason Score	(n=79)
≤6	12 (15.2%)
7	32 (40.5%)
8-10	35 (44.3%)
Seminal vesicle invasion	(n=86)
No	24 (27.9%)
Yes	62 (72.1%)
Nodal status	(n=87)
Negative	47 (54.0%)
Positive	40 (46.0%)
Positive surgical margin	(n=87)
No	5 (5.7%)
Age at Surgery	
N	(n=87)
Median	65.0 (IQR: 58-69)
Pre-op PSA (ng/mL)	
N	(n=76)
Median	12.2 (IQR: 5.7-34.9)
Race	(n=87)
Caucasian	67 (77.0%)
Other	1 (1.1%)
Undetermined	19 (21.8%)

We then further stratified patient's risk of SP by pathological Gleason score, and lymph node status. As such, the Kaplan-Meier analysis with the log rank test showed that for patients with pT4 tumors, both higher Gleason score and positive lymph node status showed differences in progression between the groups. The 10-year SP--free survival for patients with a pT4 Gleason 8-10 tumor was 47%, versus 72% for patients with a Gleason 7 tumor and 82% for patients with Gleason 6 disease (p=0.028) (Figure-2). Likewise, the 10-year SP-free survival for patients with positive lymph nodes was 45%, versus 81% for pT4N0 tumors (p=0.002) (Figure-3).

Moreover, on multivariate analysis (Table-2), positive lymph node status was found to be marginally significantly associated with patient's risk of BCR [HR 1.94, p=0.05], while both positive lymph nodes [HR 2.96, p=0.02] and higher pathological Gleason score [HR 1.95, p=0.03] were associated with a significantly increased risk for systemic progression in these men. Ten-year survival estimates for BCR, SP and OS grouped by pathological Gleason Score, median prior PSA and receipt of prior treatment are shown in Table-3.

DISCUSSION

We report the natural oncological outcomes of patients with pT4 disease treated with RP. In this cohort, we found that over one-third of patients remained free of BCR at 10 years after surgery, while the 10-year overall survival for these men was 70%. In addition, we noted that both high pathologic Gleason score and lymph node involvement contributed to the development of metastatic disease in these men.

While the outcomes for patients with locally-advanced prostate tumors treated with surgery

Figure 1 - Kaplan-Meier plot showing 10-year Overall Survival, Systemic progression and biochemical recurrence.

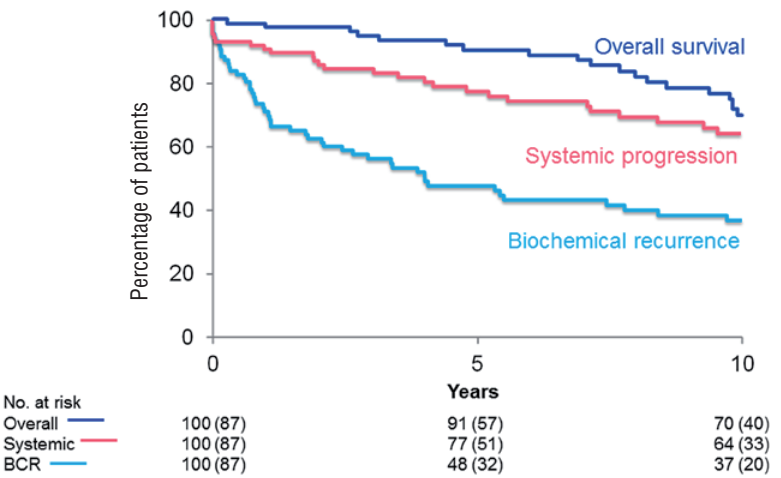
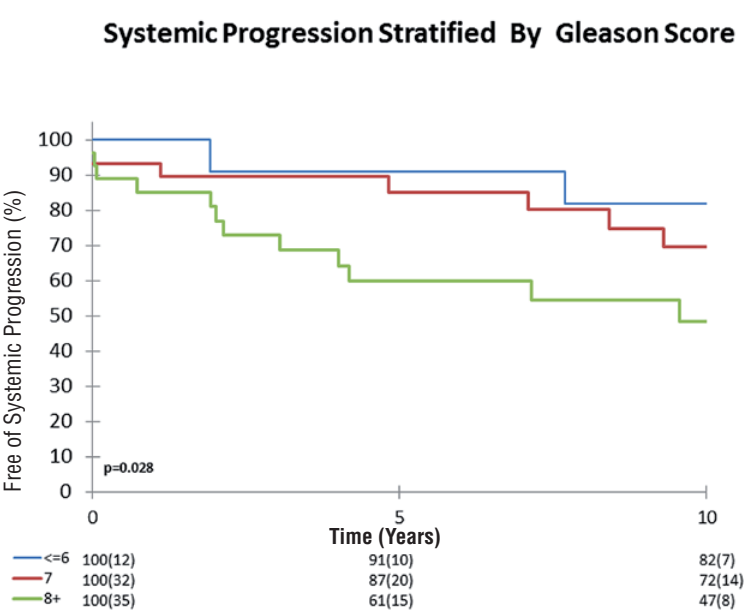


Figure 2 - Kaplan-Meier plot showing Systemic-progression stratified by Gleason-score.



have been previously described, (7, 10, 13) these series have primarily focused on T3 tumors and, as such, the present study represents what is, to our knowledge, the first report to specifically focus on pT4 prostate cancer treated with RP. Likewise, while prior series have reported long-term survival following surgery in patients with lymph-node positive disease (14), our data further provide evidence of a role for surgery in the setting of very high-risk prostate cancer. Indeed, even in patients with pT4N1 disease, the highest-risk patients, nearly half of such men were without evidence of clinical metastases at 10 years after RP.

Figure 3 - Kaplan-Meier plot showing Systemic-progression stratified by nodal status.

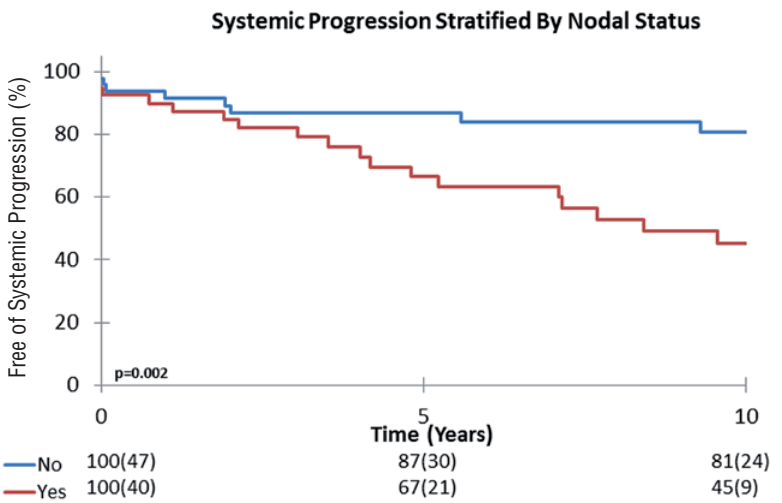


Table 2 - Multivariate analysis of factors associated with biochemical recurrence, systemic progression and all-cause mortality.

	Biochemical Failure (46 events)			Systemic Progression (27 events)			Death (29 events)		
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Path Gleason Score Group	1.17	(0.78-1.75)	0.42	1.95	(1.04-3.60)	0.03	1.06	(0.61-1.81)	0.83
Log 2 preoperative PSA (doubling)	1.13	(0.95-1.36)	0.15	0.94	(0.74-1.19)	0.65	1.14	(0.88-1.47)	0.30
Treatment prior to RP	1.62	(0.89-2.94)	0.11	1.85	(0.83-4.13)	0.12	1.003	(0.44-2.28)	0.99
Positive lymph nodes	1.94	(1.01-3.72)	0.05	2.96	(1.20-7.29)	0.02	1.37	(0.60-3.11)	0.44
Seminal vesicle invasion	1.36	(0.64-2.87)	0.42	3.91	(0.86-17.63)	0.07	1.76	(0.62-5.03)	0.28

Table 3 - Survival estimates for biochemical recurrence, systemic progression and overall survival.

	10-year Survival Estimates for Biochemical recurrence (%)	10-year Survival Estimates for Systemic Progression (%)	10-year Survival Estimates for Overall Survival (%)
Path Gleason Score			
<=6	47	82	73
7	42	72	78
8+	24	47	68
PSA (ng/DL)			
<=12.2	41	64	76
>12.2	35	66	68
Prior Treatment			
No	49	73	70
Yes	11	45	69

Level-1 data exist regarding the role of EBRT and androgen deprivation therapy (ADT) in management of locally advanced prostate cancer. In Bolla et al. trial, out of 415 patients, 89% were high risk (cT3/T4) with reported 5 year-OS in combined EBRT/ADT group to be 79% compared to 62% in the radiotherapy group alone (5). In the SPCG-7/SFUO-3 trial, 880 patients, predominantly cT3N0M0, were randomly assigned to either ADT or ADT with EBRT. Ten-year OS was better in the EBRT/ADT arm compared to ADT only arm (70% vs. 60%) (3). Both these trials provided evidence supporting addition of local radiotherapy to endocrine treatment had an important effect on overall and cancer-specific mortality in locally advanced prostate cancer. Importantly, these studies confirm the critical role of local tumor control in addition to systemic therapies.

Because of the heterogeneous population of locally-advanced prostate cancer and lack of data from randomized trials comparing RP and EBRT, definitive inferences cannot be reached regarding the relative effectiveness of each treatment modality for achieving long-term cancer control. There have been few retrospective comparative studies; while 2 studies have shown superior biochemical relapse-free survival with EBRT in comparison to RP, (15, 16) one study has shown better metastasis-free survival (17) and another studying showing better overall survival with RP compared to EBRT/ADT (18).

Interestingly, Thompson et al. evaluated 1,286 men with metastatic disease from the Southwest Oncology Group Study 8894 and determined that patients who underwent RP prior to developing metastatic disease had lower risk of death than patients who did not (HR 0.77 [0.53, 0.89]) (19). Multiple hypotheses may be offered to support a benefit for RP in advanced stage prostate cancer, including prevention of development of metastatic disease from primary tumor (19).

Zelefsky et al. (17) reviewed a cohort of 2,380 patients who either underwent RP or EBRT and evaluated them for systemic progression-free survival and cancer-specific survival (CSS). On their multivariate analysis, RP was found to be associated with reduced risk of developing metastatic disease in comparison to EBRT, especially in high-risk patients (HR 0.35; $p<0.001$).

In addition, as the management for patients with locally advanced prostate cancer is likely to involve a multi-modal approach, RP as the initial treatment affords accurate pathologic staging, which may thereby guide the selective application of secondary therapy. That is, up to 25% of patients with clinical T3 tumors in fact have organ-confined disease at surgery (20). As such, RP may facilitate the identification of patients with pathologic extraprostatic disease who might benefit from adjuvant RT (21) as well as patients with positive lymph nodes, who might benefit from adjuvant ADT (22). Further, as the extension of locally advanced tumors may result in debilitating loco-regional symptoms including recurrent hematuria, pelvic pain, as well as urinary, rectal and ureteral obstruction, the durable local control with surgery noted here (only 11.5% of the patients have experienced a local recurrence) may improve patient's quality of life as well. Indeed, a higher rate of hospital admissions, rectal or anal procedures, and open surgical procedures has been noted in patients treated with radiotherapy for prostate cancer versus patients treated with surgery (23).

Primary RP with PLND remains the only method that provides conclusive pathological evidence and excellent loco-regional control as shown by low local recurrence rate of 11.5% in our study. With data from the Southwest Oncology Group (SWOG 8794) for the use of adjuvant radiation therapy in high-risk patients (21), and Messing trial results demonstrating an advantage in survival for long-term ADT in lymph node-positive patients (22), good pathologic data are an important step toward multi-modality approach. Admittedly, the optimal management for patients with locally advanced prostate cancer remains to be determined, ideally in a prospective clinical trial setting. Nevertheless, there remains an absence of comparative level I evidence. We recognize that our study is limited by its retrospective design. Further, although the entity of pT4 disease at RP is uncommon, we acknowledge the relatively small patient sample size here. Likewise, it must be acknowledged that this cohort represents a highly

selective cohort of patients, and, as noted above, the optimal treatment for such men remains to be determined. Nevertheless, we believe that surgery represents a component of the often multi--modal approach for locally advanced prostate cancer, and may be associated with favorable long-term survival.

In conclusion, radical prostatectomy with pelvic lymph node dissection in the setting of locally advanced prostate cancer is associated with durable loco-regional control and definitive pathologic staging, which in turn facilitates the selective application of secondary therapies. As such, surgical resection should continue to be considered in the multi-modal treatment approach to these men.

CONFLICT OF INTEREST

None declared.

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Laparoscopic Radical Cystectomy in the Elderly – Results of a Single Center LRC only Series

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ABSTRACT

Objective: To compare outcome of laparoscopic radical cystectomy (LRC) with ileal conduit in 22 elderly (≥75 years) versus 51 younger (<75 years) patients.
Materials and Methods: Analysis of prospectively gathered data of a single institution LRC only series was performed. Selection bias for LRC versus non-surgical treatments was assessed with data retrieved from the Netherlands Cancer Registry.
Results: Median age difference between LRC groups was 9.0 years. (77.0 versus 68.0 years). Both groups had similar surgical indications, body mass index and gender distribution. Charlson Comorbidity Index score was 3 versus 4 in ≥50% of younger and elderly patients. Median operative time (340 versus 341 min) and estimated blood loss (<500 versus >500mL) did not differ between groups. Median total hospital stay was 12.0 versus 14.0 days for younger and elderly patients. Grade I-II 90-d complication rate was higher for elderly patients (68 versus 43%, p=0.05). Grade III-V 90-d complication rate was equal for both groups (23 versus 29%, p=0.557). 90-d mortality rate was higher for elderly patients (14 versus 4%, p=0.157). Median follow-up was 40.0 months for younger and 57.0 months for elderly patients. Estimated overall and cancer-specific survival at 5years. was 46% versus 35% and 64% versus 64% for younger and elderly patients respectively.
Conclusions: Our results suggest that LRC is feasible in elderly patients, where a non--surgical treatment is usually favoured.

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Cystectomy; Geriatrics; Minimally Invasive Surgical Procedures; Survival; Urinary Bladder Neoplasms

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INTRODUCTION

Bladder cancer (BC) rates are highest in people aged 75-84 years old (years), with a median age of 73 at diagnosis (1). Since life expectancy is still rising in Europe and the United States a decline in the incidence of BC in the elderly is not to be expected (2, 3). Open radical cystectomy (ORC) is the reference standard in the treatment of muscle invasive bladder cancer (MIBC) (4). Whether this surgical approach should also be used in the elderly is an ongoing debate (5-7). Non-surgical approaches, such as (chemo) radiation, are considered an alternative in frail or elderly patients (6). Minimal invasive procedures such as laparoscopic radical cystectomy (LRC) might, also in elderly patients, tilt the balance to surgery (8-12). We assessed morbidity and mortality in elderly patients undergoing LRC with ileal conduit and compared outcomes for younger (<75years) and elderly (≥75years) patients.

PATIENTS AND METHODS

From September 2006 until February 2013, 80 consecutive patients underwent LRC with a standard pelvic lymph node dissection (PLND) at Maxima Medical Center, Veldhoven, the Netherlands. Indications included: (1) MIBC cT2–4a, cN0-1, Nx, cM0; (2) BCG-resistant high-risk and recurrent non-MIBC (Tis, T1G3), and (3) extensive papillary disease that could not be controlled with transurethral resection and intravesical therapy alone. Patients who underwent salvage cystectomy (n=1) or received urinary diversions other than ileal conduit (n=6) were excluded. Seventy-three patients were included. To evaluate possible selection bias for surgery vs. other treatment modalities, data concerning primary treatment modalities applied, age and comorbidity for all patients diagnosed with ≥cT1-4 N0-3, x M0-1, x BC at our hospital within the study period were retrieved from the Netherlands Cancer Registry. This nationwide registry obtains notification of cancer diagnoses via PLAGA (the national network and registry of histopathology and cytopathology in the Netherlands) and independent clerks collect data from patient files.

This registration does not apply the Charlson Comorbidity Index (CCI), but scores one point per category if cardiovascular disease, hypertension, pulmonary disease, diabetes or a previous malignancy is present. There was no selection between ORC and LRC, since only LRC was performed at our hospital. The surgical technique used at our hospital has been described previously (13). A single surgeon performed the first 53 procedures and during the remainder of the procedures another surgeon was trained by the principle surgeon (only small steps, e.g. lymph node dissection, ileal conduit). During the study period the principle surgeon performed a total of 630 laparoscopic oncological procedures. First follow-up visit was 6 weeks after the procedure and at 6-month intervals including medical history, physical examination and routine hematological and biochemical laboratory examination. Abdominal ultrasonography and chest X-ray were performed every 6 months and a chest and abdomen CT-scan annually, unless otherwise clinically indicated. Follow-up was conducted at least for 90 postoperative days in our own center.

An arbitrary cut-off age of ≥75years. was used to define elderly patients (n=22) (5, 14). Baseline characteristics, perioperative and follow-up data were gathered prospectively and analyzed retrospectively. The following perioperative parameters were assessed: operative time, estimated blood loss (EBL), the number of blood transfusions, conversions, intensive care unit admissions, total length of hospital stay (LOS) and 30- and 90-d mortality. Operative time was defined as the time from incision to final closure, blood loss was estimated via collection of the suction device and LOS was calculated as the time from surgery until clinical discharge in days. Postoperative complications within 90 days after surgery were classified according to the modified Clavien system and were retrospectively registered from patient files and prospectively at follow-up visits by the second author (surgeon) of this manuscript (15). Overall survival (OS) and Cancer specific survival (CSS) were assessed for all patients as to July 2015. Survival times were defined as the time elapsed from LRC to the date of death (OS) or death of bladder cancer (CSS). Statistical analyses were performed by using SPSS statistical software (version 19.0; SPSS Inc., Chicago, Ill., USA). Survival was estimated with the Kaplan-Meier method and the Log-rank test to compare survival between groups. Values were considered statistically significant at $p<0.05$.

RESULTS

Patient characteristics are presented in Table-1. Twenty-two (30%) out of 73 patients were ≥75years. The median age difference compared to patients <75years. was 9.0 years. (77.0 vs. 68.0, $p<0.001$). There were no significant differences regarding gender, Body Mass Index (BMI), surgical indications and neoadjuvant treatments between groups. The CCI score in ≥50% of patients was one point higher in the elderly (3 vs. 4, $p<0.001$), even when points attributed

Table 1 - Pre-, per-, and postoperative patient characteristics.

	Total N = 73	< 75 years N = 51	≥ 75 years N = 22	P-value
Gender, n (%)				
Male	59 (80)	42 (82)	17 (77)	0.613[a]
Female	14 (19)	9 (18)	5 (23)	
Age (year), median (range)	70.1 (42-86)	68.0 (42-74)	77.0 (75-86)	<0.001[b]
BMI[e] (kg/m^2), median (range)	25.7 (16.0-37.6)	25.4 (16.0-37.6)	26.4 (17.3-36.0)	0.799[c]
CCI[f] (age included), (range)	≥3.0 in 50% of patients (0-8)	≥3.0 in 50% of patients (0-5)	≥4.0 in 50% of patients (3-8)	<0.001[b]
CCI[f] (age score excluded), (range)	≥0.0 in 50% of patients (0-5)	≥0.0 in 50% of patients (0-3)	≥1.0 in 50% of patients (0-5)	0.028[b]
Indication, n (%)				
NMIBC[g]	16 (22)	9 (18)	7 (32)	0.179[a]
MIBC[g]	57 (78)	42 (82)	15 (68)	
Neoadjuvant chemotherapy, n (%)	2 (3)	2 (4)	0 (0)	1.0[d]
Operative time (min), median (range)	340 (260-780)	340 (260-510)	341.0 (271-780)	0.852[b]
Estimated blood loss (mL), median (range)	500 (100-3300)	500 (100-3300)	500 (100-2000)	0.346[b]
Pre-operative Hemoglobin (mmoL/L) median (range)	8.4 (5.1-10.3)	8.8 (5.10-10.3)	7.6 (6.0-7.6)	0.004[c]
Transfusions during hospital stay, n (%)	21 (29)	10 (20)	11 (50)	0.01[a]
Conversions, n (%)	0 (0)	0 (0)	0 (0)	>0.05[d]
Intensive care unit admissions, n (%)	16 (22)	10 (20)	6 (27)	0.468[a]
Total hospital stay (days), median (range)	13.0 (6-147)	12.0 (6-147)	14.0 (8-28)	0.133[b]
Mortality, n (%)				
30 days	1 (1)	1 (2)	0 (0)	1.0[d]
90 days	5 (7)	2 (4)	3 (14)	0.157[d]
Complications 90-days n (%)				
Clavien I/ II (incl. transfusions)	37 (51)	22 (43)	15 (68)	0.05[a]
Clavien I/ II (excl. transfusions)	26 (36)	15 (29)	11 (50)	0.092[a]
Clavien III/ IV/ V	20 (27)	15 (29)	5 (23)	0.557[a]

[a] Chi-square test; [b] Mann-Whitney U test; [c] Independent sample T test; [d] Fischer's exact test; [e] Body Mass Index; [f] Charlson Comorbidity Index; [g] (N) MIBC = (Non) Muscle Invasive Bladder Cancer; [h] One or more complications per patient per category (Clavien grade I-II or III-V)

for age were distracted (0 vs. 1, p=0.028). Regarding total BC population, patient's aged ≥75years. who underwent cystectomy were significantly younger than patients who underwent other treatment modalities (p<0.001), but had similar comorbidity scores (p=0.334) as scored by the Nederlands Cancer Registry, Table-2. In total, 50% of patient's ≥75years. with cT2-4N0M0 disease and a comorbidity score of 2.0 in ≥50% underwent cystectomy. This comorbidity score

Table 2 - Primary treatment for cT1-4 N0-3,x M0-1,x bladder cancer patients at our hospital from September 2006 until February 2013 in relation to age and comorbidity. Data derived from the Netherlands Cancer Registry.

Overall (n=208)					
	Cystectomy	Radiotherapy and/ or chemotherapy	Transurethral resection and/ or intravesical therapy	No treatment	Unknown
N (%)	77 (37)	30 (14)	90 (43)	9 (4)	2 (1)
Age year[a] (median)	69.0	74.0	74.0	84.0	70.0
Comorbidity score[b]	≥1.0 in 50% of patients	≥2.0 in 50% of patients	≥1.0 in 50% of patients	≥3.0 in 50% of patients	-

Patients aged ≥ 75 years (n=85)					
	Cystectomy	Radiotherapy and/ or chemotherapy	Transurethral resection and/ or intravesical therapy	No treatment	Unknown
N (%)	22 (26)	13 (15)	44 (52)	6 (7)	-
Age year[c] (median)	77.5	85.0	82.0	87.5	-
Comorbidity score[d]	≥2.0 in 50% of patients	≥2.0 in 50% of patients	≥2.0 in 50% of patients	≥2.5 in 50% of patients	-

[a] Independent sample T-test for age at cystectomy vs. radiotherapy and/ or chemotherapy p=0.016; [b] Independent sample T-test for comorbidity at cystectomy vs. radiotherapy and/ or chemotherapy p=0.008; [c] Mann-Whitney U test for age at cystectomy vs. radiotherapy and/ or chemotherapy p<0.001; [d] Mann-Whitney U test for comorbidity at cystectomy vs. radiotherapy and/ or chemotherapy p=0.334

Note: Comorbidity was scored for: cardiovascular disease, hypertension, pulmonary disease, diabetes and previous malignancy. If present, 1 point per category was scored. Please note, this is not the Charlson Comorbidity Index Score.

was equal for patients who underwent other treatment modalities or no treatment (p=0.299).

Perioperative outcome parameters are presented in Table-1. While median operative time and EBL did not differ significantly between groups, the percentage of patients that received a blood transfusion differed (20 vs. 50%, p=0.006). The median pre-operative hemoglobin level was however significantly lower in the elderly (8.8 vs. 7.6mmoL/L, p=0.004). In both groups no conversions were needed. The percentage of intensive care unit admissions and median LOS were not significantly different between groups. One patient <75years. died within 30 days after surgery vs. none of the elderly patients (p=1.0). Within 90 days in total 2 and 3 patients died in the younger and elderly group, respectively (p=0.157). The number of patients who experienced ≥1 treatment related grade I-II complication within 90 days after surgery was higher in the group of elderly patients (68 vs. 43%, p=0.05). This in contrast to the grade III--V complication rate, which was equal in both groups (29 vs. 23%, p=0.557). Complications per patient group are shown in Table-3.

Pathology results are presented in Table-4. In both groups main histologic tumor type was urothelial carcinoma. Non-organ confined disease (≥pT3) was slightly more prevalent in the elderly (45 vs. 55%, p=0.458), as was the percentage of patients with lymph node involvement (29 vs. 32%, p=0.558) and the percentage of positive surgical margins (PSM) (8 vs. 23%, p=0.118). The mean numbers of lymph nodes removed were 15.7 and 13.3, respectively. Median overall follow-up was 40.0 months for younger and 57.0 months for elderly patients. OS and CSS were equal for both groups (Log rank p-value of 0.668 and 0.868, respectively). Estimated OS and CSS at 5years. was 46% vs.

Table 3 - Complications within 90 days after laparoscopic radical cystectomy for younger (<75 years) and elderly (≥75 years) patients according to the modified Clavien classification system.

Clavien grade	Complication	Cases (N)	Management
<75 years (N=51)			
Peroperative			
I	Damage to iliac vein	1	Laparoscopic suturing
I	Rectal lesion	3	Laparoscopic suturing
Iva	Rupture of lumbar vein	1	Laparoscopic suturing
≤ 90 days			
I	Anemia	10	Blood transfusion
I	Delirium	1	Antipsychotics
I	Wound infection	2	Antibiotics and bedside management
II	Acute myocardial infarction	1	Pharmacological treatment
II	Deep venous thrombosis	1	Pharmacological treatment
II	Exacerbation COPD	1	Pharmacological treatment
II	Pneumonia	4	Antibiotics
II	Prolonged bowel ileus (no acceptance of oral intake 5 days after surgery)	6	Conservative
II	Urinary tract infection/ sepsis	4	Antibiotics
IIIa	Ureteroileal obstruction with or without infection	2	Nephrostomy (and antibiotics)
IIIa	Lymphatic leakage with or without infection	2	Percutaneous drainage
IIIa	Necrosis of praeputium penis	1	Surgery
IIIb	Compartment syndrome lower leg	2	Surgery
IIIb	Iatrogenic corpus alienum (drain) in the abdomen	1	Surgery
IIIb	Iatrogenic defect ileal conduit after correction incisional hernia	1	Surgery
IIIb	Iatrogenic pneumothorax	1	Surgery
IIIb	Incisional hernia (+ after relaparotomy)	3	Surgery
IIIb	Rectourethral fistula	2	Surgery
Iva	Acute tubular necrosis	1	Haemodialysis
Iva	Ileal anastomotic leakage	2	Surgery
IVb > V	Pneumosepsis	1	-
IVb > V	Candida sepsis	1	-
≥75 years (N=22)			
Peroperative			
I	Rectal lesion	1	Laparoscopic suturing
I	Damage to iliac vein	1	Laparoscopic suturing
≤ 90 days			
I	Anemia	11	Blood transfusion
I	Delirium	1	Antipsychotics
I	Temporary paresis of right upper arm	1	Conservative
I	Wound infection	1	Antibiotics and bedside management
II	Atrial flutter	1	Pharmacological treatment
II	Pneumonia	3	Antibiotics
II	Prolonged bowel ileus (no acceptance of oral intake 5 days after surgery)	2	Conservative
II	Urinary tract infection/ sepsis	2	Antibiotics
IIIa	Uretero-ileal obstruction with or without infection	4	Nephrostomy (and antibiotics)
IIIa	Lymphatic leakage with or without infection	1	Percutaneous drainage
IIIb	Rectourethral fistula	1	Surgery
Iva	Rabdomyolysis	1	Conservative

Please note that some patients had more than one complication, which were all registered separately. E.g. pneumonia, delirium and prolonged bowel ileus in one patient.

Table 4 - Pathology results.

	Total N = 73	< 75 years N = 51	≥ 75 years N = 22	P-value
Histology, n (%)				
Urothelial carcinoma	71 (98)	50 (98)	21 (96)	0.515[a]
Squamous cell carcinoma	1 (1)	0 (0)	1 (4)	
Bladder sarcoma	1 (1)	1 (2)	0 (0)	
Organ confining, n (%)				
Organ-confined disease (≤ pT2)	38 (52)	28 (55)	10 (45)	0.458[b]
Non organ confined disease (>pT3)	35 (48)	23 (45)	12 (55)	
Lymph nodes removed, mean	14.9 (1-36)	15.7 (1-32)	13.3 (3-36)	0.063[c]
Lymph node involvement, n (%)				
pN0	50 (69)	35 (68)	15 (68)	
pN1	9 (12)	5 (10)	4 (18)	0.558[b]
pN2 or N3	13 (18)	10 (20)	3 (14)	
unknown	1 (1)	1 (2)	0 (0)	
Positive surgical margins, n (%)	9 (12)	4 (8)	5 (23)	0.118[a]
Median follow-up, months (range)	46.0 (0-97)	40.0 (0-97)	57.0 (1-75)	0.445[c]

[a] Fischer's exact test; [b] Chi-square test; [c] Mann-Whitney U test

35% and 64% vs. 64% for younger and elderly patients, respectively. Kaplan-Meier curves are presented in Figure-1.

DISCUSSION

ORC is considered the gold standard in the treatment of high-risk non-MIBC and MIBC (4). Analysis of currently outdated 1992 Surveillance, Epidemiology, and End Results (SEER) data showed RC was only performed in 14% of patients with MIBC aged >75years. Moreover, patients <75years., classified ASA 1-2 or ASA 3-4 were 3 to 12 times more likely to undergo radical cystectomy (RC) than those ≥75years. (16). More recent linked SEER and Medicare data (1992-2002) showed a slight increase with RC performed in 21% (17). In the Netherlands, RC is performed in less than 30% of patients aged ≥>75years. with clinical stage II-III BC (18%), in our cohort this was 50% (18). In a cohort of 3262 patients with MIBC aged >65years., elder age at diagnosis (>80 vs. 66-69years), a higher CCI score (3 vs. 0-1) and a long travel distance to an available surgeon (>50 vs. 0-4 miles) were significantly associated with decreased chance of undergoing RC (17). The 5-year adjusted OS and CSS rates for cystectomy vs. chemotherapy and/or radiation or surveillance were 42%, 21%, 15% and 67%, 48%, 43%, respectively; however, this was never assessed in a prospective randomized fashion (18). The SEER-database study of Chamie et al. showed a 6 and 20 months OS and CSS benefit in the very elderly (≥80years) undergoing RC with PNLD compared to those receiving bladder sparing treatments with radiotherapy (19). In the group of elderly actually undergoing RC, further important predictors of OS are performance and nutritional status. In a group of 152 patients aged ≥70years., a Karnofsky Performance Status (KPS) of 90-100 was associated with a 9-month OS benefit compared to a KPS <80, irrespective of chronological age (20). Poor nutritional status can increase 90-d mortality even up to 17% (21). The Eindhoven Cancer Registry data (1995-2009) of 2445 pa-

Figure 1 – A) Overall survival for laparoscopic radical cystectomy for younger vs. elderly.

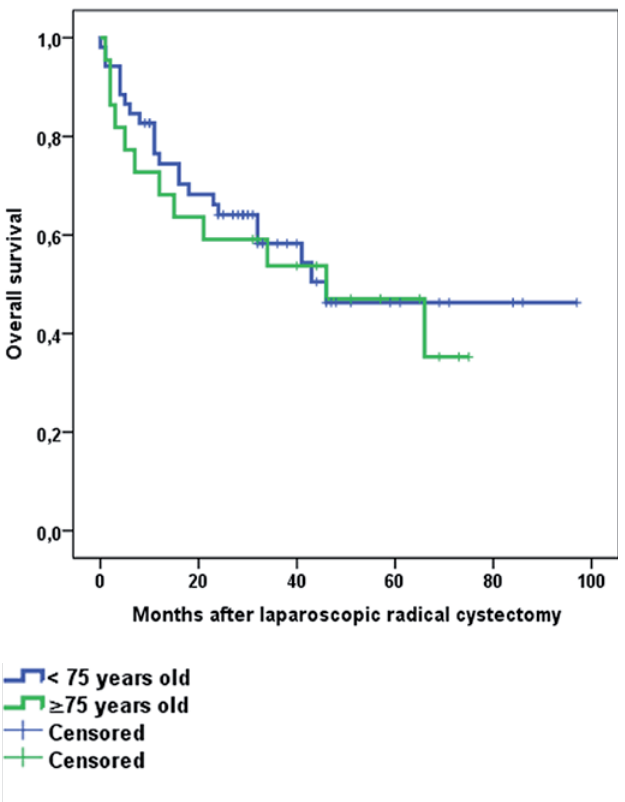
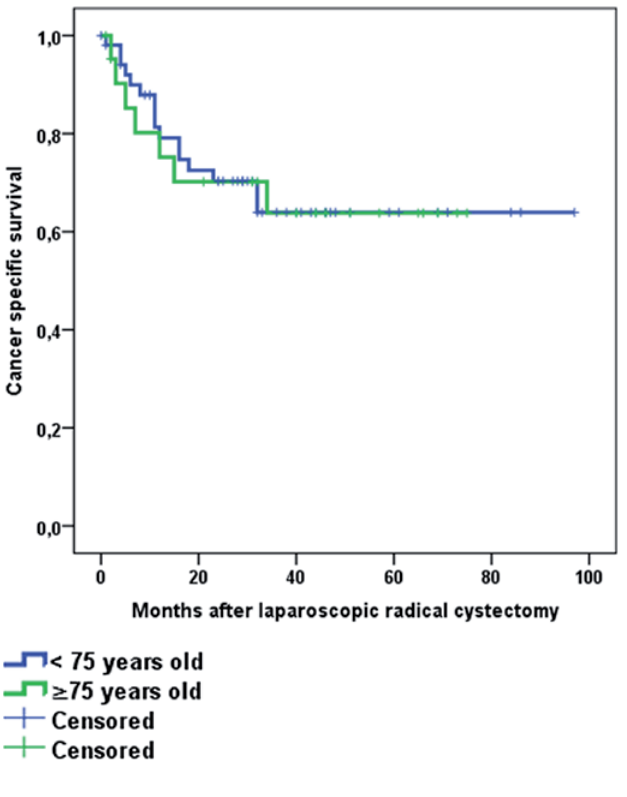


Figure 1 – B) Cancer specific survival for laparoscopic radical cystectomy for younger vs. elderly.



tients with MIBC underline before mentioned statistics, since also in our region RC was significantly associated with better OS, independently of age, socioeconomic status and serious comorbidity (22). The above-mentioned study results have to be interpreted with great caution since randomized controlled trials between RC and (multimodal) organ-preserving therapies are lacking.

Exact reasons for withholding RC in the elderly are unknown, but a combination of biological and quality of life factors is most likely. A recent multicenter validation study on the prognostic value of patient age in RC with PLND involving 4429 patients (1979-2008) showed that higher age was significantly associated with advanced pathologic tumor stages, higher tumor grades, lymph node invasion and a higher number of PSMs. This trend was also seen in our elderly population (Table-3). In categorical multivariable regression analyses adjusted for tumor grade, tumor stage, margin status, lymph node status, lymphovascular invasion and adjuvant chemotherapy, only age >80years. was significantly associated with worse CSS and OS rates compared to the younger. OS was also significantly worse for those aged >60years., remarkably CSS was not, which is in line with our oncological outcome results (23).

Another possible barrier is the urologist, who is reluctant to perform the operation and is unwilling to refer patients to someone who is (24). It is the high complication and mortality rates which may discourage surgeons from performing RC in the elderly (5, 7, 16, 17, 19). Not unreasonable considering complication rates of 30-60% (25, 26). In a center of excellence even 64% of patients, regardless of age, developed at least one complication within 90 days after surgery (27). Sound comparison between centers is however hardly possible due to heterogeneous definitions of complications (5). A recently published

randomized controlled trial of open, laparoscopic and robotic radical cystectomy reported a significantly lower 30-d complication rate in the LRC group than in the ORC group (12). The 90-d complication rate showed a trend towards fewer complications in the LRC group (12). These findings may be of special importance in frail elderly patients. In our series elderly were more prone to develop grade I-II (68 vs. 43%), but not grade III-IV complications (23 vs. 29%). This is in line with the study results of Guillotreau et al. (28). They studied 146 patients who underwent minimal invasive RC (131 LRC's) and showed grade I-II and grade III-V 90-d complication rates of 71 vs. 89% and 29 vs. 10% for younger (<70years) vs. elderly (≥70years) patients, respectively. Zeng et al. reported grade I-II and grade III-V 90-d complication rates in 38 vs. 92% and 5 vs. 16% for 21 LRC vs. 25 ORC patients aged >75years., respectively (29). In our study no remarkable differences in type of complications were seen between groups, except for the higher percentage of uretero-ileal obstructions in the elderly (6 vs. 18%), which warrants further investigation.

Perioperative mortality is an important indicator of surgical quality and might indicate the feasibility of novel techniques. The 14% 90-d mortality rate in our elderly population can be considered high, but patients did not decease due to surgery itself and resection margins were clean (Table-5). Moreover, population-based studies report 90-d mortality rates after RC in the elderly of 9 up to 15% (5, 7, 30). Recently, the European Association of Urology (EAU)-section of Uro-technology (ESUT) reported comparable long-term oncological outcome for LRC (N=503) and contemporary ORC series (8). Selection bias for LRC vs. ORC and LRC vs. other treatment modalities in elderly could, in contrast to our series, not be excluded. The ESUT study included, among others, all patients presented in the current manuscript. Sub analysis for elderly patients was however not conducted (8). Extending the 90-d follow-up period in our series did not significantly change OS and CSS rates for elderly vs. younger patients (Figure-1), independent of the median age difference of 9.0 years, worse CCI-scores adjusted for age and worse pathological outcome results, Table-4. Since PSM-status is one of the most important predictors of survival and in general is present in 6-7% of patients treated with RC, our PSM--status in 11% of the total study population is a point of concern (22, 31). However, 78% of patients with a PSM in our population had non--organ confined disease. Altogether the study results of our LRC series are not completely in line with the systematic review results of Froehner et al. who concluded that next to mortality, morbidity is also increased in elderly patients undergoing ORC (5).

Morbidity is especially related to the urinary diversion, but no randomized controlled studies comparing ileal conduits with neobladder diversions have been performed (4). However, since it is estimated that complication rates for neobladder diversions are higher than for ileal conduits we excluded patients with a neobladder diversion from analyses. Being all younger, results would be biased in favor of elderly patients. Due to limited experience with neobladder diversions, only 11% of the younger patients in our series received a neobladder diversion. Currently,

Table 5 - Characteristics of patients who died within 90 days after surgery.

	Age	CCI[a]	Pathology	Period to death	Cause of death
1	77	6	pT3N1 R0	< 90-d	Metastatic disease
2	79	4	pT3N1 R0	< 90-d	Gastro-enteritis with dehydration
3	80	5	pT3N2 R0	< 60-d	Metastatic disease
4	67	3	pT2N0 R0	< 30-d	Postoperative pneumosepsis
5	70	3	pT4N1 R1	< 60-d	Metastatic disease

[a] Charlson Comorbidity Index

guidelines state it is not possible to recommend a particular type of diversion (4).

In contrast to ORC, outcome data for LRC in the elderly is still sparse (28, 29). From aforementioned preliminary retrospective studies, it seems that in experienced hands minimal invasive surgery for MIBC in the elderly is feasible (28, 29). However, all studies so far lack insight in total bladder cancer population and the distribution of the given treatment modalities in relation to age, comorbidity scores, nutritional and performance status. Altogether selection bias for the application of minimal invasive techniques cannot be excluded. For the near future improvements in the above mentioned factors, results of controlled trials and confirmation of long-term oncological outcome results have to be waited before more definitive conclusions can be drawn and to accept a more widespread application of minimal invasive surgery for MIBC in younger and elderly patients.

Our study results are subjected to the limitations and biases of retrospective analyses of a prospective database and the small number of elderly patients. Selection bias for surgery in the elderly cannot be excluded, but seems to be relatively small regarding the distribution of applied treatment modalities in total bladder cancer population in relation to age and comorbidity (Table-2). Moreover, 50% of patients in our cohort aged ≥75years. with clinical cT2-4N0M0 BC underwent radical cystectomy. An important limitation is the absence of an ORC control group. This study, in contrast to many others, however excludes selection bias between LRC and ORC and shows comparable outcome result for elderly vs. younger patients undergoing LRC. Based on the aforementioned RCT results of Khan et al. (12) and our data we assume that minimal invasive procedures may tilt the balance to surgery in elderly patients.

CONCLUSIONS

Our results suggest that LRC is feasible in elderly patients, where a non-surgical treatment is usually favoured.

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CONFLICT OF INTEREST

None declared.

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Prognostic features for quality of life after radical cystectomy and orthotopic neobladder

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ABSTRACT

Purpose: To analyse prognostic features on quality of life (QoL) following radical cystectomy and urinary diversion via orthotopic neobladder in a single-centre patient cohort.
Materials and Methods: Postoperative QoL of 152 patients was assessed retrospectively using the validated QLQ-C30 questionnaire. Potential associations of patient's quality of life including pre-and intraoperative characteristics, surgeon experience, postoperative time course, adjuvant therapies, and functional outcome were defined a priori and evaluated. Mann-Whitney-U-, Kruskal-Wallis-, Spearman correlation and post hoc-testing were used. A multivariate analysis using a multiple logistic regression model was performed. A p value <0.05 was considered to be statistically significant.
Results: Median follow-up was 48 months. Univariate analysis of prognostic features for health-related QoL revealed a significant impact of gender (p=0.019), performance status (p<0.001), experience of surgeon (>100 previous cystectomies, p=0.007), and nerve-sparing surgery (p=0.001). Patients who underwent secondary chemotherapy or radiotherapy had significant lower QLQ-C30 scores (p=0.04, p=0.02 respectively). Patients who were asymptomatic had a significantly higher quality of life (p<0.001). A significant impact of severity of incontinence based on ICIQ-SF score (p<0.001) and daily pad usage (p<0.001), existence of daytime incontinence (p<0.001), existence of urgency symptoms (p=0.007), and IIEF-5 score (p<0.001) could be observed. In multivariate analysis, independent prognostic relevance could be confirmed for preoperative ECOG performance status of 0 (p=0.020 vs. ECOG 1, p=0.047 vs. ECOG 2), experience of the respective surgeon (≥100 vs. <100 previous cystectomies, p=0.021), and daytime continence (p=0.032).
Conclusion: In the present study, we report health-related QoL outcomes in a contemporary patient cohort and confirm preoperative ECOG status, surgeon experience and daytime incontinence as independent prognostic features for a good postoperative QoL.

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Keywords:
Quality of Life; Cystectomy; Urinary Bladder Neoplasms; Urinary Incontinence

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INTRODUCTION

Bladder cancer is the second most common malignancy in the urinary tract and transitional cell carcinoma of the urinary bladder is currently the fourth most common malignancy in men in the Western world (1). Neoadjuvant chemotherapy, followed by radical cystectomy, extended pelvic lymphadenectomy, and urinary diversion (using an ileal conduit or ileal orthotopic neobladder) is the gold standard therapeutic approach for muscle invasive bladder cancer (2). However, radical cystectomy comes along with quite a burden for the patient considering a long-term morbidity-rate of

up to 90% leading to a considerable mortality rate (3-5). Recently, there was an increasing interest in QoL aspects for patients undergoing radical cystectomy, mostly regarding different types of urinary diversion (6). While short-term and long--term complications and long-term functional outcomes after urinary diversion via orthotopic neobladder have been extensively analysed there is still a lack of data concerning QoL aspects. Functional outcomes have been described to significantly influence the patient's QoL after orthotopic urinary diversion, but little is known about further possible influencing factors (7). Thus, the aim of this study is to investigate various potential contributing factors on patient's QoL after radical cystectomy and urinary diversion via orthotopic neobladder.

MATERIALS AND METHODS

Patient population, study design and data assessment

In one tertiary care centre, 301 cystectomies with urinary diversion via orthotopic neobladder were performed between May 2004 and September 2014 by a total number of 14 surgeons. During follow-up period, 92 patients had died. After approval by an institutional review board, data assessment was performed retrospectively via standardized questionnaires that were sent to 209 patients who underwent radical cystectomy and urinary diversion via orthotopic neobladder due to malignancy. Questionnaires were returned by 152 patients and underwent further analysis. This leads to a global response rate of 50.5%.

Health-related QoL was measured using the standardized EORTC QLQ-C30 (global health status; validated German version) (8). The global health status was calculated following current EORTC instructions: score=100* [(question29+question30)/2–1]/6 (9). This indicates that higher scores are associated with an increased QoL.

Potential predefined prognostic features of patient's QoL were evaluated. Hereby we focused on various categories including preoperative characteristics (gender, preoperative age, performance status), intraoperative features (surgeon's experience, nerve sparing operation, operation duration, blood loss, blood transfusion, postoperative revision, postoperative complications), TNM classification, functional outcome (continence status, urgency symptoms, sexual function), adjuvant therapies (chemotherapy, radiotherapy), and symptoms (any symptoms, night sweats, weight loss, flank pain).

The preoperative performance status was determined based on the respective Eastern Cooperative Oncology Group performance (ECOG) status score (10).

Daytime continence was determined using the validated International Consultation on Incontinence Questionnaire (ICIQ) short-form scoring system in a validated German translation, and pad usage (11). The existence of urgency symptoms was assessed. Depending on the respective ICIQ-SF, patient's stress urinary incontinence was classified as mild (1-5), moderate (6-10), and severe (>10) as previously described (11).

Sexual function was assessed using the abridged International Index of Erectile Function (IIEF-5) (12) and abridged Female Sexual Function Index (FSFI-6) (13) respectively. A cut-off score of >20 (out of 25) points was used as the definition of potency as previously described (12). Female sexual dysfunction was defined by a FSFI-6 of less than 18 as previously described by Isidori et al. (13).

Statistical analysis

Primary endpoint was the QoL (global health status based on EORTC QLQ-C30 questions 29 and 30) of the respective patient. Secondary endpoints were above-mentioned prognostic features. Analysis was performed using the global health status as a continuous variable as well as using a cut-off score of 70 as recently described by Snyder et al. (14). Hereby, a QLQ-C30 score of less than 70 is associated with a poor quality of life, a score of at least 70 is considered to be associated with a good quality of life.

To analyse and compare QoL in the respective subgroups, Mann-Whitney-U-, Kruskal--Wallis-ANOVA, and chi-squared-Test, Spearman's rank correlation, and post-hoc-testing were used whenever indicated. Additionally, a multiple lo-

gistic regression model that included all potential prognostic features that showed significant results in the univariate analysis was performed. All statistical analyses were performed using STATISTICA 10 software (StatSoft, Tulsa, OK, USA). A p value <0.05 was considered to be statistically significant.

RESULTS

Pre-and perioperative patient characteristics

Median follow-up, defined as time between radical cystectomy and answering of the questionnaire, was 48 months [3-108]. Follow-up was within the first 12 months in 22% (n=33) of the patient collective. Median patient age was 71 years [44-88 years]. Patient characteristics of the patients that underwent further analysis are summarized in Table-1.

Analysis responder vs. non-responder

To analyse for a potential selection bias, we compared preoperative characteristics and pathological tumour stage for those patients who responded to the questionnaire and those who did not respond. Among the patients who did not respond to the questionnaire, 56% were deceased. Median

Table 1 - Baseline patients characteristics, histopathologic results, and stated symptoms following radical cystectomy and orthotopic urinary diversion after a median follow-up of 48 months.

Gender		
	Male	87.5% (133/152)
	Female	12.5% (19/152)
Age at follow-up (years)		
	Median	71 (range 44 to 88)
pT-Stage		
	pTis	22.4% (34/152)
	pT1	23.0% (35/152)
	pT2	27.6% (42/152)
	pT3	18.4% (28/152)
	pT4	4.6% (7/152)
Lymphadenectomy performed		
	Yes	91.4% (139/152)
	No	8.6% (13/152)
pN-Stage		
	pN0	89.2% (15/139)
	pN+	10.8% (15/139)
Symptoms at follow-up		
	Yes	34.2% (50/146)
	No	65.8% (96/146)
	Unknown	3.9% (6/152)
	Flank pain	15.1% (22/146)
	Night sweats	6.2% (9/146)
	Weight loss	4.1% (6/146)
	Other	8.9% (13/146)

age was 65 years for both groups (p=0.400). Regarding the non-responder group, 48% had a locally advanced disease (pT3-4) (responder: 25%, p<0.001), and 30% had lymph node infiltration during cystectomy (responder: 12%, p<0.001). There were no significant differences regarding the ratio of high-grade tumours (non-responder: 90% vs. responder: 86%, p=0.359), metastatic disease (9% vs. 9%, p=0.971), and (concomitant) carcinoma in situ (39% vs. 48%, p=0.108).

Functional outcome

Median ICIQ-SF within our patient collective was 10 (1-21). Depending on the respective ICIQ-SF scores, incontinence was classified as severe in 44% (n=67) of our study group. Regarding pad usage, 40% (n=61) were in need of more than 2 pads daily. Incontinence results are summarized in Table-2.

Data concerning sexual function was available for 126 out of 133 male patients and for 15 out of 19 female patients. Analysis of the respective IIEF-5 scores showed a median IIEF-5 of 3 (1-24) within our study collective. Regarding the female patients, median FSFI-6 was 4 (1-20). Sexual function results are summarized in Table-2.

Univariate analysis of prognostic features for health-related QoL

Preoperative characteristics

At median follow-up, overall health-related QLQ-C30 was 75 for male patients and 67 for female patients (p=0.019). Patients with less or equal 71 years (median age of the patient collective) had a median QLQ-C30 of 69, whereas patients older than 71 years had a median score of 74 (p=0.784). Analysing patient's age continuously using Spearman's correlation, we found no statistically significant impact on the respective QoL (p=0.926). Regarding the preoperative performance status, we found patients with a preoperative ECOG score of 0 having a significantly higher QoL compared to patients with a preoperative ECOG score of 1 or 2 (p<0.001 respectively, Figure-1A).

Intraoperative characteristics

QoL for patients whose cystectomy was performed by an experienced surgeon (>100 previous

Table 2 - Functional outcome following radical cystectomy and orthotopic urinary diversion after a median follow-up of 48 months.

ICIQ-SF at follow-up		
	Median	10 (range 4 to 21)
Severity of incontinence based on ICIQ-SF		
	Mild (1 - 5)	16.4% (25/152)
	Moderate (6 - 10)	37.5% (57/152)
	Severe (>10)	44.1% (67/152)
	Dry	2.0% (3/152)
Pad usage at follow-up		
	0-1	37.5% (57/152)
	2	22.3% (34/152)
	>2	40.1% (61/152)
IIEF-5 at follow-up		
	Median	3 (range 1 to 24)
	Unknown	5.2% (7/133)
	>20	5.6% (7/126)
	≤20	94.4% (119/126)
FSFI-6 at follow-up		
	Median	4 (range 1 to 20)
	Unknown	21,1% (4/19)
	>18	13,3% (2/15)
	<18	86.7% (13/15)

ICIQ-SF = International Consultation on Incontinence Questionnaire short-form; **IIEF-5** = International Index of Erectile Function; **FSFI-6** = abridged Female Sexual Function Index

radical cystectomies) had a median QLQ-C30 score of 83 whereas patients whose radical cystectomies were performed by a less experienced surgeon (<100 previous radical cystectomies) had a median QLQ-C30 score of 74 (p=0.186, Figure-1B). However, when using the predefined cut-off value, 53% (experienced) vs. 35% (less experienced) of the patients had a QLQ-C30 score of >70 (p=0.019).

A nerve-sparing radical cystectomy was performed in 77 of 152 patients (50.7%). If a nerve-sparing operation was performed, median postoperative QoL was significantly increased (QLQ-C30 82 vs. 69; p=0.001, Figure-1C). 64% of the nerve-sparing group had a QLQ-C30>70 (vs. 36%, p<0.001).

There were no statistical significances regarding intraoperative complications (44 vs. 50% QLQ-C30≥70, p=0.731), postoperative complications (49 vs. 51%, p=0.744), need for perioperative blood transfusion (36 vs. 53%, p=0.116), intraoperative blood loss (<500mL: 55% QLQ-C30≥70 vs. ≥500mL: 47%, p=0.355), and the operation duration (median operation time: 217 minutes; <217 minutes: 58% QLQ-C30≥70 vs. 43%, p=0.077).

Regarding the pathological tumour stage, patients with locally advanced disease (pT3-4) as well as patients with lymph node involvement did not have statistically significant different QLQ-C30 scores than those with limited disease as well as without lymph node involvement (p=0.760, p=0.632 respectively).

Postoperative time course and adjuvant therapies

Regarding the postoperative time course, we found no statistically significant differences when comparing patient's QOL after 3 months, 6 months, 9 to 12 months, 1 year, 2 to 3 years, 4 to 5 years, and more than 5 years postoperatively. In detail, patients who were analysed during their first year of follow-up had a median QLQ-C30 of 67 (39% QLQ-C30≥70); patients who were analysed after more than one year postoperatively had a median score of 75 [p=0.078 (53% QLQ-C30≥70, p=0.168)].

Adjuvant systemic chemotherapy or palliative chemotherapy due to tumour recurrence was performed in 19 of 152 patients (12.5%). Median QLQ-C30 score for those patients was 67 (vs. 82 if no chemotherapy was performed, p=0.04). Among the patients who underwent chemotherapy, 33% had a QLQ-C30 of ≥70 (vs. 52%, p=0.174). There was no significant difference if the chemotherapy was performed within the last 12 months before answering the questionnaire, or more than 12 months ago (p=0.635).

During the postoperative time course, radiotherapy was performed in 5 of 152 patients (3.9%). Median QLQ-C30 was 77 if no radiotherapy was performed, and 41 if radiotherapy was performed (p=0.006). None of the patients who underwent radiotherapy reached a QLQ-C30 score of ≥70 (p=0.02).

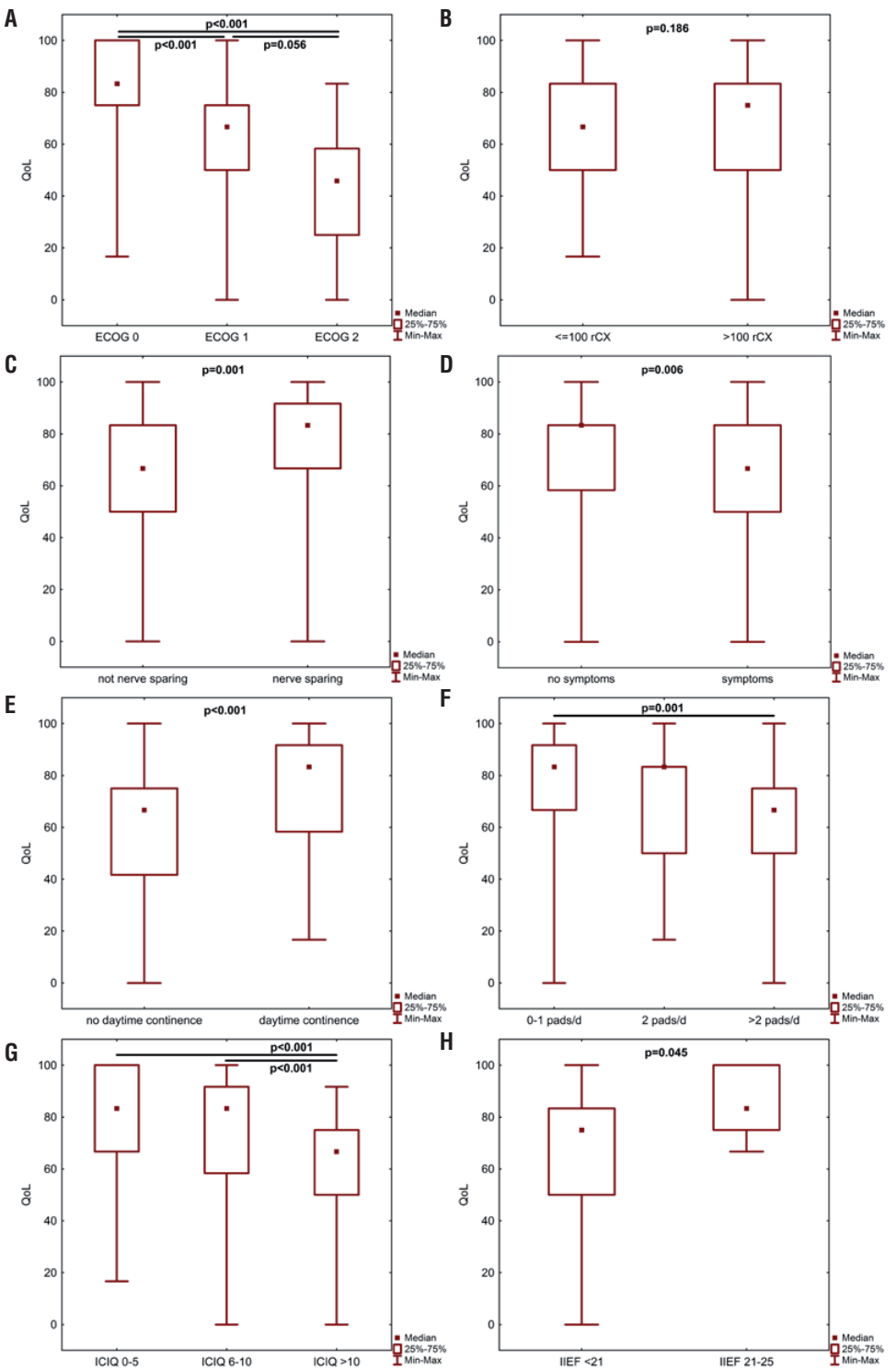
In total, 19 patients (12.5%) suffered from recurrence of their malignancy. There was no statistically significant difference when comparing these patients with those patients without recurring disease (41% QLQ-C30≥70 vs. 52%, p=0.462).

Patients who were symptomatic at the time of follow-up had a significantly lower QoL than those being asymptomatic (p=0.006, Figure-1D). In detail, patients suffering from weight loss had a significantly lower QoL than asymptomatic ones (p=0.003) whereas patients with night sweats as well as flank pain did not (p=0.076, p=0.214 respectively). The symptomatic as well as asymptomatic patients did not differ in terms of disease extent and lymph node involvement (p=0.800). Among the asymptomatic patients, 60% had a QLQ-C30 of ≥70 (symptomatic patients: 34%, p=0.003).

Functional outcome

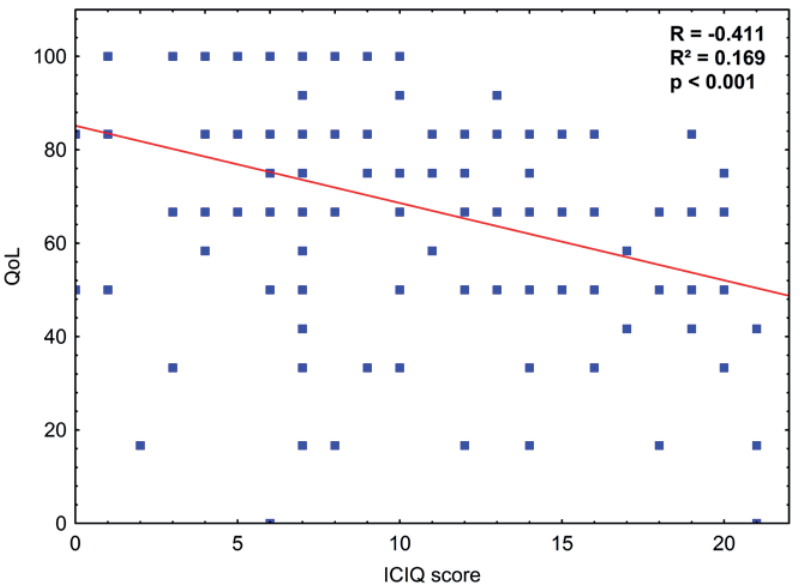
Addressing the potential impact of incontinence, we found a median QLQ-C30 of 69 for daytime incontinence and a median QLQ-C30 of 82 for daytime continence (p<0.001, Figure-1E). Impact of severity of incontinence was analysed based on daily pad usage [0-1 pad (83) vs. >2 pads (65), p<0.001, Figure-1F], and based on the ICIQ-SF [dry/mild incontinence (median QLQ-C30: 83) vs. moderate incontinence (83) vs. severe incontinence (67), p<0.001, Figure-1G]. Continuous analysis of the respective ICIQ-SF scores confirmed our primary results (p>0.001, Figure-2). Among the dry patients as well as patients with mild incontinen-

Figures 1 A-H – Univariate analysis of multiple predefined prognostic features on postoperative QoL after radical cystectomy and orthotopic urinary diversion.



A p value <0.05 was considered statistically significant (**ECOG**=Eastern Cooperative Oncology Group performance status score; **ICIQ-SF**=International Consultation on Incontinence Questionnaire short-form; **IIEF-5**=International Index of Erectile Function; **QoL**=quality of life; **rCx**=radical cystectomy).

Figure 2 - Impact of patient's ICIQ-SF score on health-related quality of life based on EORTC QLQ-C30 global health status using Spearman's rank correlation. A p value <0.05 was considered statistically significant (QOL=quality of life).



ce, 69% had a QLQ-C30 score of ≥70 (moderate incontinence: 66%, severe incontinence: 28%; p<0.001). In line, 65% of the patients in need of 0-1 pads per 24h had a QLQ-C30 score of ≥70 (2 pads: 62%, >2 pads: 30%; p<0.001). Among the patients that achieved daytime continence, 61% had a QLQ-C30 score of ≥70 (no daytime continence: 28%, p<0.001). Patients suffering from urinary urgency had a median QLQ-C30 of 70, whereas patients with no urgency symptoms had a median score of 82 (p=0.015). Regarding the predefined cut-off values, 28% of the patients suffering from urinary urgency achieved a QLQ-C30 score of ≥70 (no urgency symptoms: 55%, p=0.007).

Analysis of sexual outcome revealed a significant influence of IIEF-5 [<20 (median QLQ-C30: 75) vs. >20 (83), p=0.045, Figure-1H], but not of FSFI-6 (FSFI-6≤18 vs. FSFI>18; p=0.800). The patient subgroup that skipped the IIEF-5 questionnaire did not differ statistically significant in age (p=0.786) as well as ICIQ-SF (p=0.863) to those who answered the questionnaire. Among the patients with an IIEF-5 score of 20-25, 86% achieved a QLQ-C30 score of ≥70 (<20: 51%, p=0.078).

Multivariate analysis of prognostic features for health-related QoL

In a last step, a multivariate analysis was performed using a multiple logistic regression model. Hereby, all prognostic features that had statistically significant results in the univariate analysis were included. In detail, independent prognostic relevance could be confirmed for preoperative ECOG performance status of 0 (p=0.020 vs. ECOG 1, p=0.047 vs. ECOG 2), the experience of the respective surgeon (≥100 vs. <100 previous cystectomies, p=0.021), and daytime continence (p=0.032). Results of the multivariate analysis are summarized in Table-3.

DISCUSSION

Orthotopic ileal neobladder has become a widespread treatment of muscle-invasive bladder cancer. Certainly, complication rates are still high and functional outcomes may be unfavourable even in high-volume centres (15-18). As a consequence, recently more attention was drawn towards health-related QoL after radical cystectomy (6). However, measurement of QoL remains difficult and requires specific tools to address

Table 3 - Multivariate analysis of prognostic features that showed significant results in univariate analysis.

Prognostic feature	P value	OR	95% CI	
Gender [male/female]	0.185	2.745	0.618	12.193
ECOG 1 vs. 0	**0.020**	0.336	0.134	0.842
ECOG 2 vs. 0	**0.047**	0.121	0.015	0.974
ICIQ group mild vs. moderate	0.394	1.76	0.48	6.449
ICIQ group mild vs. severe	0.382	0.504	0.109	2.342
Surgeon experience <100 vs. >100 prev. rCx [y/n]	**0.021**	3.442	1.203	9.847
Nerve-sparing [y/n]	0.165	2.029	0.747	5.511
Radiation therapy [y/n]	0.999	0	0	.
Symptoms [y/n]	0.109	0.458	0.176	1.192
Urge [y/n]	0.259	0.486	0.139	1.702
Daytime continence [y/n]	**0.032**	3.131	1.101	8.908
Daily pad usage 2 vs. 0-1	0.817	0.859	0.238	3.105
Daily pad usage >2 vs. 0-1	0.995	0.996	0.274	3.616

CI = confidence interval; **ECOG** = Eastern Cooperative Oncology Group performance status score; **ICIQ** = International Consultation on Incontinence Questionnaire; **OR** = odds ratio; **rCx** = radical cystectomy.
A p value >0.05 was considered statistically significant.

health-related QoL aspects adequately. A various number of different existing instruments-generic, cancer specific and bladder cancer specific--complicate the comparison and integration of the pre-existing literature (19). We used the validated EORTC QLQ-C30 that has been frequently used in multiple studies investigating QoL after radical cystectomy (20-27). In recent years, many efforts have been made to define certain cut-off values in order to select those patients with unmet needs for further support. Snyder et al. evaluated more than 500 oncologic patients and found a QLQ-C30 global health status cut--off value of 70 to have a sensitivity of up to 86% and a negative predictive value of up to 94% (14, 28). The aim of the current study was to evaluate various potential prognostic features on patients QoL after orthotopic urinary diversion, focusing on preoperative, perioperative as well as postoperative features. To allow a better comparison with existing literature, we analysed the postoperative QLQ-C30 global health status as a continuous parameter as well as following Snyder et al. (14).

Addressing patient-derived features, we found no statistically significant impact of preoperative patient's age. This finding is in line with recent publications indicating that radical cystectomy with orthotopic urinary diversion can be safely performed even in elderly patient cohorts (29). Imbimbo et al. even found significant increased QLQ-C30 scores in patients older than 65 years (30). However, there is also evidence that elderly patients are still less likely to receive orthotopic urinary diversion (31). Going further, we found a significant impact of the preoperative performance status on postoperative QoL in univariate as well as in multivariate analysis. Given the fact that health-related QoL measurements take into consideration multiple aspects including physical status, general health and social interaction, it seems intuitive that patients with a better performance status profit more from a procedure that aims to allow an unaltered, active lifestyle. In line, it has been shown that patients undergoing orthotopic urinary diversion are more active and have a better physical function compared to patients undergoing incontinent urinary diversion (32). Our observations indicate that age per se is not associated with impaired QoL after orthotopic urinary diversion and discussion of QoL aspects prior to radical cystectomy should

be based on the patient's performance status rather than on the respective patient's age. Regarding preoperative patient selection, our results indicate, that elderly patients who have an adequate performance status, can be treated with an orthotopic urinary diversion and still have a good postoperative QoL. Since radical cystectomy for octogenarians becomes more accepted, this finding has important clinical implications (33).

In the current study, various intraoperative characteristics on the patient's postoperative QoL were analysed, indicating a significant impact of the surgeon's experience both in univariate as well as in multivariate analysis. To our knowledge, evidence regarding the surgeon's learning curve impact on patients postoperative QoL after radical cystectomy and orthotopic urinary diversion is still very limited. However, there is evidence that excellent functional outcomes can be achieved in high-volume centers (18). In line, it has been shown that the surgeon's individual learning curve has a significant impact on functional outcome after radical prostatectomy and is therefore directly affecting the patient's postoperative QoL (34). The impact of surgeon's experience on postoperative QoL after orthotopic urinary diversion might highlight the importance of the referral to high-volume centers and therefore has clinical implications.

Addressing a potential time course of patient's QoL after orthotopic urinary diversion, we found no statistically significant differences in QoL after the respective moments of follow-up. However, there was a statistical trend favouring those patients who were evaluated more than 1 year postoperatively. This might indicate that QoL increases during the postoperative course of time as described by Kulaksizoglu and colleagues (27). We found that, if patients underwent adjuvant or palliative chemotherapy or radiotherapy, QoL was significantly lower, no matter if the respective therapy was performed within 1 year before answering the questionnaires or not. It has to be stated, however, that there might be a relevant non-responder bias in our patient cohort. Thus, these findings have to be interpreted with caution. Our results are partly in line with the findings of Cognetti et al. who also found a decline of QoL after initiation of adjuvant Cisplatin-based chemotherapy. However, the authors stated that there was a subsequent improvement after the initial decline of QoL, which is not reflected by our data (35).

To assess the impact of urinary incontinence on health-related QoL, we used the validated ICIQ-SF questionnaire and pad usage and found a significant impact of urinary leakage. These findings are in line with the results of Takenaka et al. who evaluated long-term outcome in QoL after orthotopic neobladder in 86 patients and found worse QoL scores in patients with daytime incontinence (36). Zahran et al. analyzed QoL of 74 women after radical cystectomy and orthotopic neobladder using QLQ-C30 and observed a significant negative impact of incontinence (7). In line with Imbimbo et al., we found urinary incontinence being an independent prognostic feature of an impaired QoL (30). However, the findings of the current study addressing the great impact of continence are based on multiple consistent parameters in a contemporary patient collective and therefore add important information to the existing literature.

It is commonly accepted that a significant proportion of patients after orthotopic bladder replacement suffer from sexual dysfunction (37). In our patient collective, for instance, only 5.6% of the men could be classified as "no sexual dysfunction" based on the respective IIEF-5 score (>20). Since no preoperative data was available, these results have to be interpreted with caution. However, we were able to show that health-related QoL was significantly increased in those patients who had a postoperative IIEF-5 score of more than 20. To date, there is only limited data concerning the impact of sexual function on QoL after radical cystectomy. Studies from large prostate cancer series, on the other hand, consistently report better QoL outcomes for nerve-sparing radical prostatectomies indicating a major impact of sexual preservation on QoL aspects after major pelvic surgery (38). Summarizing, our findings highlight the great impact of functional aspects on health-related QoL. However, it is somewhat difficult to imply the important role that postoperative continence plays for health-related

QoL into daily clinical practice. Naturally, every surgeon tries to achieve the best possible functional result. However, one might focus on the development of continence-preserving technical modifications. Regarding radical prostatectomy for example, the posterior rhabdomyosphincter reconstruction, also known as Rocco stitch, has been proposed to improve postoperative continence (39, 40). Additionally, we still lack knowledge how the shape of the neobladder (e.g. U- vs. W-shape) affects postoperative continence recovery.

Certainly, our study is not devoid of limitations. Major drawback is its retrospective nature with all the known limitations that are inherent. The current study is a cross-sectional study and QoL has not been measured at specific time-points. Nevertheless, the current study provides QoL analyses from various different follow-up periods, providing a possible idea of the natural process of QoL after radical cystectomy. In the current study, the EORTC QLQ-C30 global health status was used. It has to be stated, that, unlike the EORTC QLQ-BLM30, this questionnaire is not bladder cancer specific and lacks additional information regarding body image, urostomy problems, and use of catheters. The QLQ-BLM30 has been used in several publications before, but is still not validated (23, 26, 41). Additionally, the Functional Assessment of Cancer Therapy-General, Bladder (FACT-BL) and Vanderbilt Cystectomy Index (FACT-VCI) are validated bladder cancer specific questionnaires that have been used in health-related QoL studies before (42). However, in a recent meta-analysis including data from 18 studies that investigated health-related QoL after radical cystectomy, 10 out of 18 used the EORTC QLQ-C30 questionnaire (43). This indicates, that, despite being not cancer specific, the QLQ-C30 questionnaire is well established in QoL analyses of patient cohorts that underwent radical cystectomy and orthotopic urinary diversion.

CONCLUSIONS

The current study analyses the impact of multiple potentially prognostic features on QoL after orthotopic urinary diversion. We report health-related QoL outcomes in a contemporary patient cohort. Hereby, we were able to show that preoperative ECOG status, surgeon experience and daytime incontinence are independent prognostic features for a good postoperative QoL.

ABBREVIATIONS

QoL = Quality of life
QLQ-C30 = Quality of life questionnaire C30
EORTC = European Organization for Research on Treatment of Cancer
ICIQ-SF = International Consultation on Incontinence Questionnaire short-form
IIEF-5 = International Index of Erectile Function
FSFI-6 = Female Sexual Function Index (abridged)
FACT-BL = Functional Assessment of Cancer Therapy-General, Bladder
FACT-VCI = Vanderbilt Cystectomy Index

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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MCM – 2 and Ki – 67 as proliferation markers in renal cell carcinoma: A quantitative and semi – quantitative analysis

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ABSTRACT

Introduction/Background: Fuhrman nuclear grade is the most important histological parameter to predict prognosis in a patient of renal cell carcinoma (RCC). However, it suffers from inter-observer and intra-observer variation giving rise to need of a parameter that not only correlates with nuclear grade but is also objective and reproducible. Proliferation is the measure of aggressiveness of a tumour and it is strongly correlated with Fuhrman nuclear grade, clinical survival and recurrence in RCC. Ki-67 is conventionally used to assess proliferation. Mini-chromosome maintenance 2 (MCM-2) is a lesser known marker of proliferation and identifies a greater proliferation faction. This study was designed to assess the prognostic significance of MCM-2 by comparing it with Fuhrman nuclear grade and Ki-67.

Material and Methods: n=50 cases of various ages, stages, histological subtypes and grades of RCC were selected for this study. Immunohistochemical staining using Ki-67(MIB-1, Mouse monoclonal antibody, Dako) and MCM-2 (Mouse monoclonal antibody, Thermo) was performed on the paraffin embedded blocks in the department of Morbid anatomy and Histopathology, University of Health Sciences, Lahore. Labeling indices (LI) were determined by two pathologists independently using quantitative and semi-quantitative analysis. Statistical analysis was carried out using SPSS 20.0. Kruskall-Wallis test was used to determine a correlation of proliferation markers with grade, and Pearson's correlate was used to determine correlation between the two proliferation markers.

Results: Labeling index of MCM-2 (median=24.29%) was found to be much higher than Ki-67(median=13.05%). Both markers were significantly related with grade (p=0.00; Kruskall-Wallis test). LI of MCM-2 was found to correlate significantly with LI of Ki-67(r=0.0934;p=0.01 with Pearson's correlate). Results of semi-quantitative analysis correlated well with quantitative analysis.

Conclusion: Both Ki-67 and MCM-2 are markers of proliferation which are closely linked to grade. Therefore, they can act as surrogate markers for grade in a manner that is more objective and reproducible.

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Keywords:
Carcinoma, Renal Cell; Ki-67 Antigen; Minichromosome Maintenance Complex Component 2; Cell Proliferation

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INTRODUCTION

Renal cell carcinoma (RCC) is the most common renal tumor accounting for 3% of cancer deaths in males (1). Fuhrman nuclear grading is the most important histological parameter to predict prognosis of the patients. Over the years Fuhrman nuclear grading has come to be accepted by most pathologists in the World. However, many studies have shown that it suffers from substantial intra-observer

and inter-observer variation. Fuhrman nuclear grade relies on three factors for its categorization: the nuclear size, nuclear pleomorphism and the nucleolar prominence. However, there is no clear guideline in cases that do not fit in any category. Most pathologists rely upon nucleolar prominence as the sole criteria for grading the tumor. The problem arises between grade II and III where pathologists have to decide whether nucleoli are large and prominent enough at low power (100X) to classify the tumor as grade III (2).

Recent evidence has suggested that Fuhrman nuclear grading has no prognostic importance in chromophobe renal tumors (3), while in papillary renal cell carcinoma only nuclear pleomorphism has any prognostic significance (4).

ISUP (International Society of Urological Pathology) published its recommendations in a meeting in 2013, where it recognized all the short comings of Fuhrman nuclear grading and proposed a new classification based on nucleolar prominence alone. However, the system does not apply to chromophobe renal carcinomas. The distinction between grade II and grade III tumors still remains subjective (5).

Therefore, there is a need for a prognostic marker that might act as surrogate for nuclear grade and be also more objective in its interpretation. Proliferation index of renal cell carcinoma as determined by Ki-67 is known to be of prognostic importance in univariate and multi-variate analysis and is known to correlate with tumor grade. Discovered by Gerdes, Ki-67 is a non-histone protein that is present in all the phases of cell cycle (G1, S, G2 and mitosis) while it is absent in non-dividing cells (G0) (6). This property makes it an excellent marker for determining the proliferation fraction of cells in tumors. Instead of relying on multiple parameters, Ki-67 requires only the presence or absence of nuclear staining as its sole criteria for interpretation. Several studies have determined a cut off value over which the expression of this marker is related with poor prognosis.

Minichromosome maintenance proteins were first reported by Maine in 1984. In an attempt to identify factors that originate DNA replication, Maine and colleagues constructed mitotically stable plasmids named minichromosomes and attempted to find mutant genes which affect the maintenance of these minichromosomes (7).

Up to 10MCM proteins have been discovered so far. This is a highly conserved group of proteins present in all eukaryotes. MCM1 is a transcription factor; MCM10 is a ring shaped hexamer which physically links Helicase to DNA polymerase during DNA replication. MCM8 has a role in mitosis, while the role of MCM9 has not been elucidated completely (8).

Here we are mainly concerned with MCM2, which forms a hexameric pre-replication complex (pre-RC) with other MCM proteins 3-7, and attaches to origin recognition complex (ORC) in association with CDC6, which acts as a recruitment factor (9). MCM2 and other proteins are also direct targets of ATM (ataxia telangiectasia mutated) and ATR (ataxia telangiectasia and Rad3 related) genes, which stop DNA replication and initiate repairs (10). MCM2 encodes a protein of 890 amino acids, and is homologous with MCM3 (11).

Several studies have shown that MCM proteins remain stable during cell cycle while their amount decreases significantly during differentiation. This is because the pre-replication complex is present throughout the cell cycle. This property makes these proteins suitable as proliferation markers (12).

Alex Freeman conducted a large study on immunohistochemical expression of MCM proteins in many normal, dysplastic and malignant tissues. Proliferation index of MCM-2 was found comparable to other proliferation markers in most normal and pathological tissue samples (13). Roddins conducted the first study on the pattern of distribution of MCM-2 in normal kidney and RCC. He found that RCC showed greater expression of this marker as compared to normal tissue. A labeling index of >20% was associated with poor prognosis (14). Dudderidge et al. 2005 compared MCM-2 with Geminin and Ki-67 and concluded that MCM-2 was a better marker than Ki-67 or Geminin to predict disease-free survival. He also suggested that semi-quantitative analysis of MCM-2 can be more easily utilized in laboratories and may act as a tool to complement Fuhrman nuclear grade to assess the prognosis of the patient more objectively. However, no attempt has been made to externally validate these results

or to perform a semi-quantitative analysis to verify these claims until now (15).

We have determined the proliferation indices of fifty cases of RCC using Ki-67 and MCM-2. We have correlated the proliferation index with Fuhrman nuclear grade. We have also compared the proliferation indices of different subtypes of renal cell carcinoma. We have also compared the results of our quantitative analysis with semi-quantitative analysis.

MATERIALS AND METHODS

Patients and archival material

Fifty cases of renal cell carcinoma were selected from Allied Hospital Faisalabad and Sheikh Zayed Hospital Lahore. Paraffin embedded blocks along with other clinical data were acquired after permission. Patient's age, gender, tumor laterality and stage of the tumor were recorded. Nephrectomy specimens obtained from recent surgeries were grossed in the Histopathology department of University of Health Sciences according to CAP guidelines. H&E slides were prepared to determine tumor subtype, Fuhrman nuclear grade and other important prognostic parameters.

Immunohistochemistry

Immunohistochemical staining using Ki-67(MIB-1, Mouse monoclonal antibody, Dako) and MCM-2 (Mouse monoclonal anti-body, Thermo) was performed on the paraffin embedded blocks. Tris-EDTA Buffer antigen retrieval solution was used and the solution heated in water bath for 2 hours. Dako peroxidase block, secondary antibody and streptavidin biotinylated essays were used. Section of a reactive lymph node was used as a positive control. Any amount of nuclear staining was considered positive. Any cytoplasmic staining was ignored. Labeling indices (LI) were determined by two pathologists independently.

For quantitative analysis first hot spots were determined using low power and then approximately 1000 cells were counted in 5 high power fields. Following formulae was used to obtain the labeling index:

$$\text{Labelling index(LI)} = \frac{\text{No. of cells stained}}{\text{Total no. of cells per HPF}} \times 100$$

Semi-quantitative analysis was performed by analyzing different fields for highest staining and then the pathologists estimated the labeling index based on the number of cells stained in one HPF. The observers were blind to the results of semi-quantitative analysis.

Statistical analysis

Statistical analysis was carried out using SPSS 20.0. Mean±S.D was given for quantitative variables like age, greatest dimension (T) and Labeling indices of Ki-67 and MCM-2. Kruskall-Wallis test was used to determine a correlation of proliferation markers with grade, and Pearson's correlate was used to determine correlation between both proliferation markers. Spearman's correlate rank was used to determine relationship among quantitative and semi-quantitative analysis of expression of both markers.

RESULTS

Patients characteristics and gross and histological features Clinical and histological details are mentioned in Table-1.

Expression of MCM-2 and Ki-67 and its relationship with Fuhrman nuclear grade.

Table 1 - Clinical and important histological parameters.

Total number of cases	50
Male	36
Female	14
Mean age	50.16 years
Mean of maximum size (T)	10.41cm
Grade I	8
Grade II	12
Grade III	14
Grade IV	16
Clear cell carcinoma	37
Papillary renal cell carcinoma	7
Chromophobe renal cell carcinoma	6

The median proliferation index of MCM-2 and Ki-67 was 13.05% and 24.29% respectively. Labeling index of Ki-67 and MCM-2 increased with grade. For Ki-67 the LI for grade I was 4.7738±3.3% (4.05%), for grade II 9.75±10.22% (median=9.2%), for grade III 13.86±9.3% (median=12.70%) and for grade IV 35.11±14.1% (median=36.93%). MCM-2 showed increased staining in corresponding grades with LI of 12.22±5.91% (median=10.96%), 16.91±12.81% (median=16.21%), 25.18±17.97% (median=22.08%) and 52.05±15.21% (median=50.99%) for grades I through IV respectively (Figures 1 and 2, Table-2A).

Figure 1 – A) H&E Renal cell carcinoma grade I. Small, round and uniform nuclei. No evident nucleoli. B) Ki-67 staining in grade I renal cell carcinoma. C) MCM-2 staining in grade I renal cell carcinoma. D) Grade 2 renal cell carcinoma. Nuclei with irregular outlines and inconspicuous nucleoli. E) Ki-67 staining in grade II renal cell carcinoma. F) MCM-2 staining in grade II renal cell carcinoma. G) Fuhrman nuclear grade III, Irregular nuclei with identifiable nucleoli at 100x magnification. H) Ki-67 staining in grade III renal cell carcinoma. I) MCM-2 staining in grade III renal cell carcinoma. J) Fuhrman nuclear grade IV, Large, hyperchromatic, pleomorphic nuclei. Single or multiple nucleoli. K) Ki-67 staining in grade IV renal cell carcinoma. L) MCM-2 staining in grade IV renal cell carcinoma.

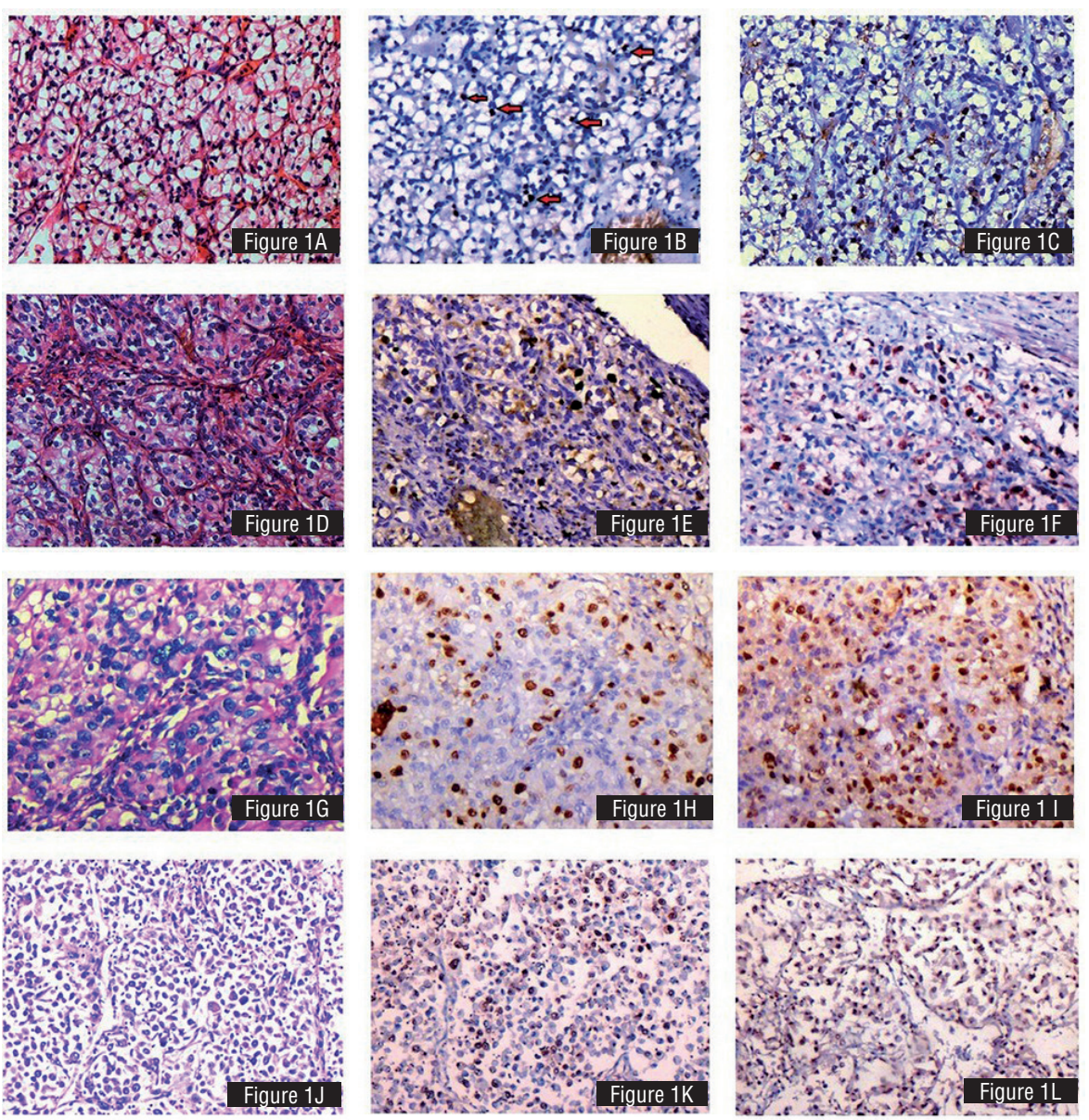
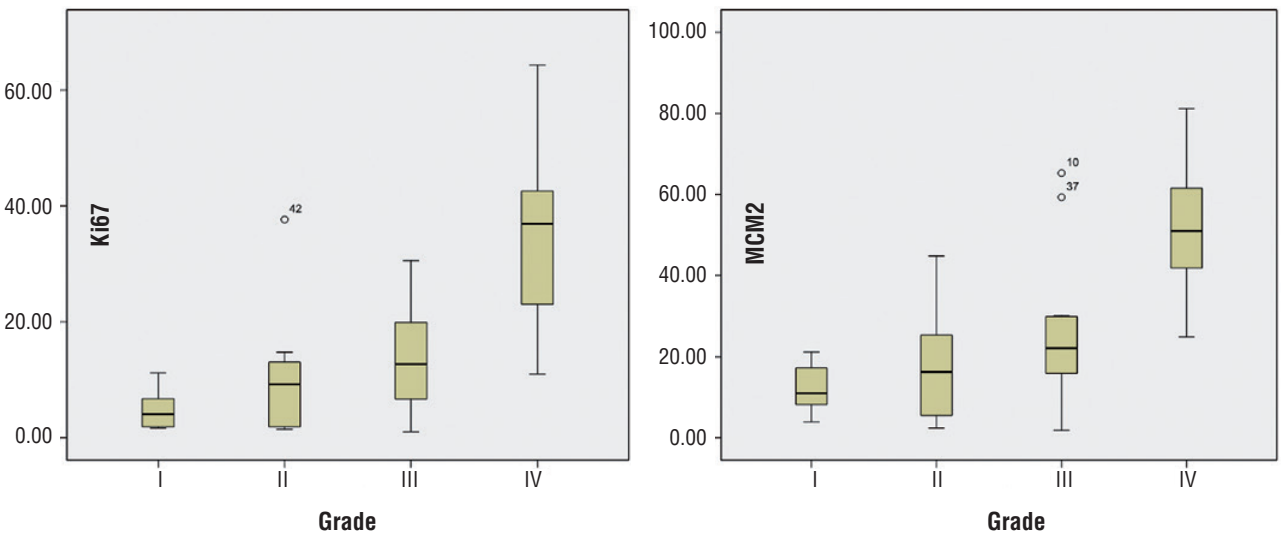


Figure 2 - Stem and Leaf graphs showing relationship of grade with Labeling index for Ki-67 and MCM-2. Note that although there is significant overlap in the LI between grades, the mean is increasing. Black central line (median), Boxes (interquartile ranges) and ranges are enclosed by lines. The outlying cases are shown by dots.



Proliferation indices were also determined separately for each tumor subtype. Labeling index was significantly lower for chromophobe tumors Ki-67=2.1±1.05% (median=1.83%); MCM-2=5.14±3.29% (median=4.35%) as compared to clear cell carcinomas Ki 67=21.43±16.39% (median=14.78%);MCM-2, 34.53±20.85% (median=27.55%), although no significant relationship was found between papillary Ki-67=15.06±14.25% (median=10.79%) ;MCM-2=25.36±19.00% (median=21.43%) and clear cell carcinomas (Table-2A).

A correlation was sought for between ki-67 and MCM2 using Pearson's correlate and Spearman's rank test. A positive correlation of r=0.934 and ρ=0.953 was obtained and was found to be significant at p=0.01. A scatter diagram was drawn to show the correlation (Figure-3).

Semiquantitative analysis of the IHC specimen was done by estimating number of labelled cells in a single HPF in the maximum labeling area. The results produced are grouped in the Table-2B. Spearman's correlation rank test was used to determine the accuracy of semiquantitative analysis. It was ρ=0.892 in Ki-67 and ρ=0.909 in MCM-2. The correlation was significant at 0.01. However, when we split the correlation in every grade we found that Ki-67 (quantitative) versus Ki-67 (semi-quantitative) was -0.051 in grade I. The correlation was insignificant with p=0.904. In comparison MCM-2 showed a correlation of ρ=0.884. The correlation between quantitative and semi-quantitative analysis of MCM-2 was significant in every grade (Table-2B).

DISCUSSION

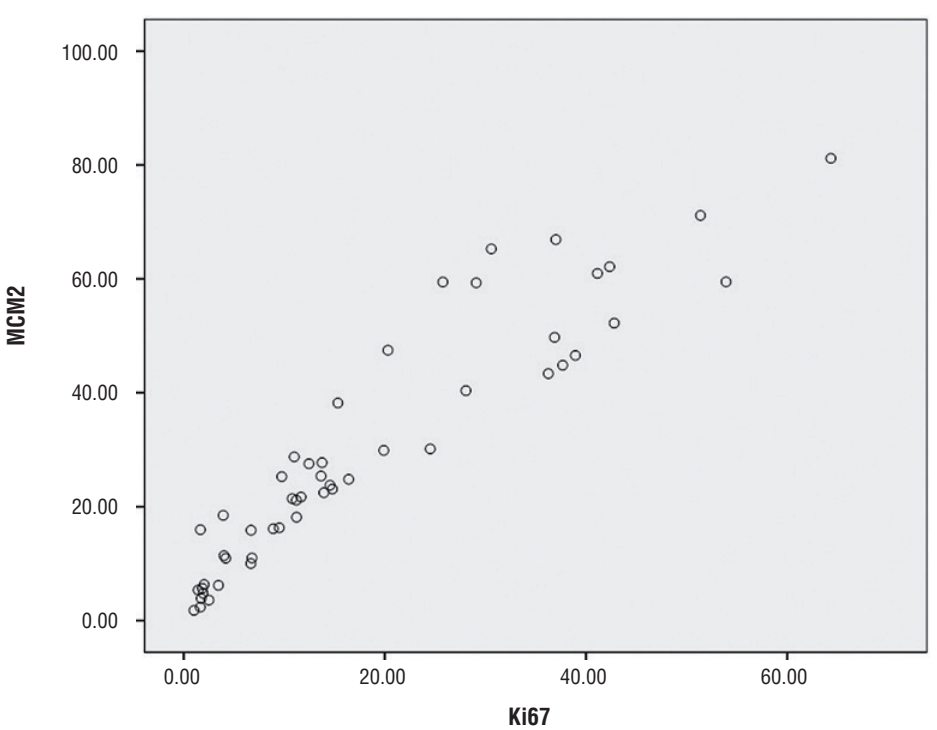
Renal cell carcinoma has the poorest prognosis among all the urological tumors. Tumor stage remains the most powerful predictor of prognosis. Among histological parameters Fuhrman nuclear grade is considered the most important prognostic parameter. Our study was dominated by high grade tumors as n=30 (60%) of the tumors were either grade III or IV. This was in contrast to a study from Karachi by Latif et al. 2011 who found 66.6% grade II tumors in their study (15). Frank et al. found 46.6% tumors in either grade III or IV (16). There is very little similarity in the percentage of tumors within each grade, as it becomes difficult to fulfill all the criteria of Fuhrman nuclear grading and the pathologist comes up with his own interpretation of the system.

Papillary renal cell carcinomas are graded better using only the criteria of nucleolar prominence

Table 2A - Breakdown of values of proliferation index according to tumour subtype and grade. There is an increase in proliferation index in clear cell renal cell carcinoma and papillary renal cell carcinoma according to grade. No such relationship is seen in the chromophobe renal tumours.Table 2B - There is remarkable correlation between quantitative and semiquantitative analysis for both markers. In group I the median value for Ki-67 is 4.05% in quantitative analysis while it is 5% in semiquantitative analysis. MCM-2 shows 10.96% in quantitative and 10.00 in semiquantitative analysis. For grade II Ki-67(quantitative) is 9.2% versus 5% in semi-quantitative. MCM-2 shows better correlation in this grade with median values of 16.21% versus 15%. In group III Ki-67(quantitative) is 12.7% and semi-quantitative is 12.5%. MCM-2 shows (quantitative)22.08% versus 20% in semi-quantitative analysis. Finally grade IV shows Ki-67(quantitative) 36.93% versus 40% in semiquantitative. MCM-2(quantitative) 50.99% versus 55% in semiquantitative. The mean values and standard deviations also correspond with each other. Note that Ki-67(semi-quantitative) median for grade I and II is same as compared to MCM-2. Spearman's Correlate is significant in all cases except for Ki-67 grade I.

		A) Correlation of grade with labelling index according to each subtype						B) Comparison of Labelling indices of Ki-67 and MCM-2 using quantitative and semi-quantitative analysis					
		Clear cell Carcinoma		Papillary Renal cell carcinoma		Chromophobe renal cell carcinoma		Ki-67 (Quantitative)	Ki-67 (Semi-quantitative	Spearman's Correlation rank test(p)	MCM-2 (Quantitative)	MCM-2 (semi-quantitative)	Spearman's correlation rank test(p)
Grade		Ki-67	MCM-2	Ki-67	MCM2	Ki-67	MCM-2						
I	N	6	6	1	1	1	1	8	8	-0.051	8	8	0.884
	Median	4.05%	13.47%	6.67%	10.02%	1.74%	3.90%	4.06%	5.00%	p=0.904	10.97%	10.00%	p=0.004
II	N	8	8	2	2	2	2	12	12	0,88	12	12	0,876
	Median	11,10%	24,19%	5,57%	9,32%	1,67%	5,08%	9,20%	5,00%	p=0.000	16.22%	15.00%	p=0.000
III	N	9	9	2	2	3	3	14	14	0.726	14	14	0.756
	Median	14.54%	23.77%	12.27%	24.58%	2.50%	3.60%	12.70%	12.50%	p=0.003	22.09%	20.00%	p=0.002
IV	N	14	14	2	2	NA	NA	16	16	0.791	16	16	0.865
	Median	36.93%	54.60%	31.55%	41.86%	NA	NA	13.05%	10.00%	p=0.00	24.29%	20.00%	p=0.000
						Total	N	50	50		50	50	
							Median	13.05%	10.00%		24.29%	20.00%	

Figure 3 - Scatter diagram showing correlation of expression between Ki-67 and MCM-2. Note that smaller increases in Ki-67 result in larger increases of MCM-2.



while Fuhrman nuclear grading seems to have no application in chromophobe renal tumors.

Ki-67 is long known to have independent prognostic importance in renal cell carcinoma, and also correlates with tumor grade. On the other hand, only a handful of studies have been previously carried out on the expression of MCM-2 in renal cell carcinoma. Ki-67 expression in our study ranged from 1.02-64.34% (median=13.05%). These results were similar to Leclercq's study (17) who recorded a range of 0-60% (median=8%) and Meierhofer et al. (2004) (18) who recorded 0-68% (median=2%). There is an overall similarity in the range of expression of Ki-67 in renal cell carcinoma. We used MIB-1 antibody in our study. However, older studies which used different versions of Ki-67 antibodies showed different results. These facts support our assumption that subjective variations have lesser role to play when assessing the expression of these immuno markers.

On the other hand, MCM-2 expression ranged from 1.80-81.80% (median=24.29%) in our study. Rodins et al. reported a range of 0.2-91.5% (median=35.7%), and Dudderidge et al. (2005) reported a range of 0.9-98.8% (median=41.6%). The expression of MCM-2 in all three studies is greater than that of Ki-67. The broader range of expression of this marker makes it relatively easier to interpret it in semi-quantitative analysis.

Our study had 6 chromophobe renal tumors. No correlation was found between their nuclear grades and proliferation index further supporting the fact that Fuhrman nuclear grade has no prognostic significance in these tumors. As a whole the proliferation index of clear cell carcinomas was greater than papillary and chromophobe renal cell carcinomas.

A good correlation was found between the proliferation indices of Ki-67 and MCM-2. MCM-2 had a greater expression than Ki-67 in nearly all the cases. Semi-quantitative analysis correlated well with the figures obtained from quantitative analysis. This suggests that objectivity of determining labeling index is largely maintained during semi-quantitative analysis and these parameters can be easily used outside of a research laboratory.

In this study we have shown that IHC expression of Ki-67 and MCM-2 not only correlates with the Fuhrman nuclear grade but is more objective and reproducible and can be used in conjunction with Fuhrman nuclear grade to determine prognosis in renal cell carcinoma.

CONFLICT OF INTEREST

None declared.

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Diagnostic Ureteroscopy for Upper Tract Urothelial Carcinoma is Independently Associated with Intravesical Recurrence after Radical Nephroureterectomy

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ABSTRACT

Purpose: To determine the effect of diagnostic ureteroscopy on intravesical recurrence in patients with upper tract urothelial carcinoma (UTUC) after radical nephroureterectomy (RNU).
Materials and Methods: We conducted a retrospective analysis of 664 patients who were treated with RNU for UTUC from June 2000 to December 2011, excluding those who had concomitant/prior bladder tumors. Of the 664 patients, 81 underwent diagnostic ureteroscopy (URS). We analyzed the impact of diagnostic ureteroscopy on intravesical recurrence (IVR) using the Kaplan-Meier method. Univariate and multivariate analyses were used to determine the independent risk factors.
Results: The median follow-up time was 48 months (interquartile range (IQR): 31-77 months). Patients who underwent ureteroscopy were more likely to have a small ($p<0.01$), early-staged ($p=0.019$), multifocality ($p=0.035$) and ureteral tumor ($p<0.001$). IVR occurred in 223 patients during follow-up within a median of 17 months (IQR: 7-33). Patients without preoperative ureteroscopy have a statistically significant better 2-year (79.3%±0.02 versus 71.4%±0.02, $p<0.001$) and 5-year intravesical recurrence-free survival rates (64.9%±0.05 versus 44.3%±0.06, $p<0.001$) than patients who underwent ureteroscopy. In multivariate analysis, the diagnostic ureteroscopy ($p=0.006$), multiple tumors ($p=0.001$), tumor size <3cm ($p=0.008$), low-grade ($p=0.022$) and pN_0 stage tumor ($p=0.045$) were independent predictors of IVR.
Conclusions: Diagnostic ureteroscopy is independently associated with intravesical recurrence after radical nephroureterectomy.

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Ureteroscopy; Oncology; Bladder; Ureter; Urinary Tract

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INTRODUCTION

Upper tract urothelial carcinoma (UTUC) is rare and accounts for only 5-10% of urothelial carcinoma cases, with an annual incidence of 1-2 cases per 100.000 in Western countries (1-3). Radical nephroureterectomy (RNU) with bladder cuff excision is the gold standard for managing UTUC (4). The incidence of subsequent intravesical recurrence (IVR) following RNU is 22-47%, which means a close follow-up using cystoscopy is required to detect the high incidence of IVR (5, 6).

Several risk factors are reported to be associated with IVR, such as the age, sex, tumor location, multiplicity, size, surgical approach (open or laparoscopic surgery) and distal ureter

management, T stage, grade, carcinoma in situ, and history of bladder cancer (7). With the development of medical devices, diagnostic ureteroscopy is becoming a powerful tool for patients with UTUC, which could contribute to the diagnostic certainty and decision making regarding treatment options. The European guidelines suggest that diagnostic ureteroscopy should be performed in the preoperative assessment of any UTUC patient (Grade C) (8). Concerns, however, have been raised that there is a possible risk of tumor implantation during ureteroscope manipulation and irrigation (9).

To the best of our knowledge, previous studies are sparse, and there is no consistent conclusion on the impact of diagnostic ureteroscopy for intravesical recurrence (9-11). Therefore, we conducted this study, based on data from a large center in China, to determine whether diagnostic ureteroscopy results in IVR after RNU.

MATERIALS AND METHODS

The follow-up data of patients with UTUC who were treated with RNU at Peking University First Hospital, Beijing, China, from June 2000 to December 2011 were reviewed. Out of 892 patients submitted to RNU in our service we selected 753 with complete FU information. Among these 753 patients, we excluded 82 patients with concomitant/prior bladder tumors, 6 patients with bilateral UTUC, and 1 patient with distant metastasis. Therefore, 664 patients were included in this study. None of these patients received neoadjuvant or adjuvant chemotherapy.

Of 664 patients, 583 in the control group were diagnosed by CT/MRI, urinary cytology specimens and retrograde pyelography. Eighty-one patients underwent diagnostic ureteroscopy and were included in the study group. Diagnostic ureteroscopy is especially used when there is diagnostic uncertainty or when conservative treatment is being considered, but there are no standardized prospective criteria. Chest X-ray and preoperative cystoscopy were performed in all patients to rule out metastasis and concomitant bladder tumors.

All patients underwent retroperitoneal open or laparoscopic nephroureterectomy. In all cases, the ureter was ligated immediately after control of the renal artery without dissecting around the kidney. The distal ureter and bladder cuff were all managed by extravesical dissection and the intramural portion within the bladder wall through an open Gibson incision. A regional lymph node dissection was performed in case of suspicious lymph node invasion on preoperative imaging or intraoperative examination.

The clinicopathologic data were retrospectively recorded. All tumors were graded by the World Health Organization classification of 2004 and staged by the Union for International Cancer Control TNM classification of malignant tumors 2002. The tumor location was defined as renal pelvis or ureter, and tumor multifocality was defined as the presence of two or more macroscopic tumors in the upper urinary tract.

During follow-up, patients received cystoscopy every 3 months for the first 2 years, which extended to 1 year thereafter. Serum creatinine level, chest X-ray and CT or MRI were performed simultaneously.

All statistical data were managed with SPSS version 19.0. Statistical significance was set at $p<0.05$. Continuous variables were compared using the two-sample t-test, and categorical variables were compared using the Chi square test. The Kaplan-Meier method was used to estimate the survival outcomes. Univariate analysis with the log-rank test and multivariate analysis with Cox proportional hazards regression model were used. Only variables that were significant according to univariate analysis were considered for the multivariate analysis.

RESULTS

The clinicopathologic features are summarized in Table-1. The median patient age was 68 years (IQR: 60-74 months). The median follow-up time was 48 months (IQR: 31-77 months). There was no significant difference in gender, age, smoking status, surgical mode, presence of hydronephrosis, presence of carcinoma in situ, N stage or tumor grade. Patients who underwent ureteroscopy were more likely to have a small ($p<0.01$), early-staged ($p=0.019$), multifocality ($p=0.035$) and ureteral tumor ($p<0.001$).

Table 1 - Clinicopathological characteristics of 664 patients with RNU for UTUC.

	URS(+) n=81	URS(-) n=583	p values
Gender			
Male	31(38.3%)	264(45.3%)	0.234
Female	50(61.7%)	319(54.7%)	
Age (years)	65.9±11.3	66.6±10.7	0.617
Smoking			
yes	10(12.3%)	111(19.0%)	0.144
no	71(87.7%)	472(81.0%)	
Surgical mode			
Laparoscopic	23(28.4%)	196(33.6%)	0.349
Open	58(71.6%)	387(66.4%)	
Tumor location			
Pelvis	26(32.1%)	342(58.7%)	P<0.001*
Ureter	55(67.9%)	241(41.3%)	
Multifocality			
Multiple	27(33.3%)	132(22.6%)	0.035*
Solitary	54(66.7%)	451(77.4%)	
Hydronephrosis			
present	45(55.6%)	329(56.4%)	0.882
absent	36(44.4%)	254(43.6%)	
Tumor size			
≥3 cm	28(34.6%)	335(57.5%)	P<0.001*
<3 cm	53(65.4%)	248(42.5%)	
Cis			
present	4(4.9%)	15(2.6%)	0.400
absent	77(95.1%)	568(97.4%)	
pT stage			
≤T2	65(80.2%)	393(67.4%)	0.019*
>T2	16(19.8%)	190(32.6%)	
N stage			
N+	3(3.7%)	44(7.5%)	0.206
N0	78(96.3%)	539(92.5%)	
Tumor grade			
Low	51(63.0%)	330(56.6%)	0.278
High	30(37.0%)	253(43.4%)	

*p<0.05, significant difference was reached

There was intravesical recurrence in 223 patients (33.6%) during follow-up within a median of 17 months (IQR: 7-33 months). The 2-year and 5-year intravesical recurrence-free survival rates for patients with and without ureteroscopy were 71.4%±0.02 versus 79.3%±0.02 and 44.3%±0.06 versus 64.9%±0.05, respectively (Figure-1).

In univariate analysis, diagnostic ureteroscopy and tumor multifocality, tumor size, tumor location, T stage, N stage and grade were all associated with intravesical recurrence while in multivariate Cox regression analysis only the diagnostic ureteroscopy (p=0.006), multiple tumors (p=0.001), tumor size <3cm (p=0.008), low-grade tumor (p=0.022) and pN_0 stage (p=0.045) were independent predictors (Table-2).

DISCUSSION

RNU with bladder cuff excision is the gold standard for managing UTUC (4). However, a high potential of intravesical recurrence after RNU has been reported. In the guidelines for NCCN, all UTUC patients after RNU are recommended to undergo cystoscopy for routine bladder surveillance (12). In this retrospective study, the incidence of IVR was 33.6%, which is in agreement with previous reports (22-47%) (5, 6). The explanation of such a high incidence of IVR can only be hypothesized, including the field cancerization hypothesis and intraluminal seeding of the tumor (13, 14).

Several studies have evaluated the risk factors for IVR after RNU, such as age, gender, tumor multiplicity, TNM stage, grade, tumor location, size, previous/concomitant bladder tumors, carcinoma in situ, surgical mode and distal ureter management (7, 15-22). Among these factors, a history of a prior bladder tumor and a multifocal primary tumor are the most frequently reported, while others are still under debate. In the present study, however, we excluded the patients with previous/concomitant bladder cancer because the incidence of IVR in those patients is related to local disease instead of UTUC or ureteroscopic

Figure 1 - Kaplan-Meier survival curves for intravesical recurrence-free survival stratified by preoperative diagnostic ureteroscopy.

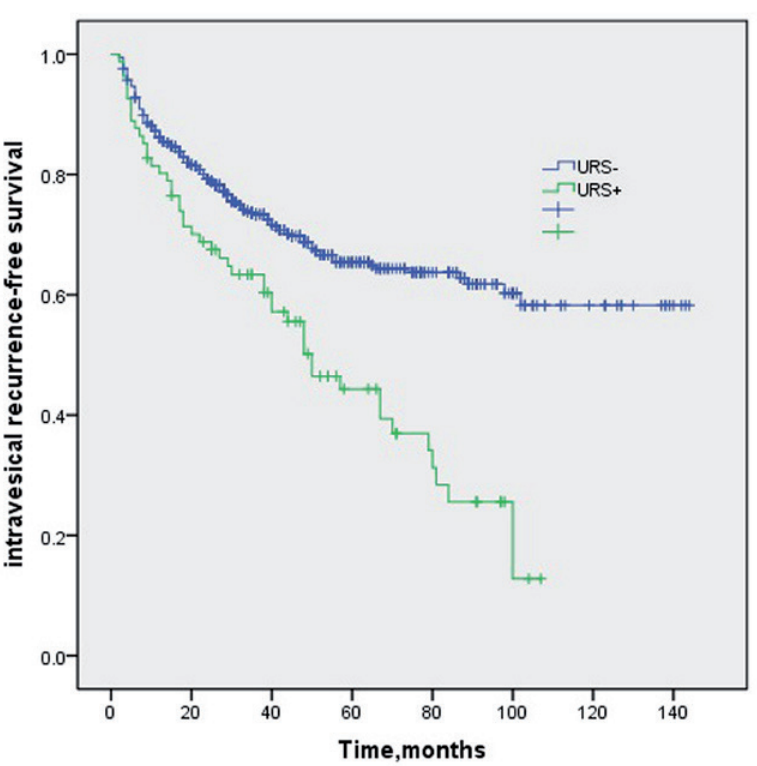

Table 2 - Univariable and multivariate Cox regression analyses predicting intravesical recurrence in 664 patients after nephroureterectomy for UTUC.

	Univariate analysis (P value)	Multivariate Cox Regression analysis		
		HR	95% CI	P
Diagnostic ureteroscopy	<0.001	1.592	1.143-2.218	0.006*
Multifocal tumor	<0.001	1.596	1.206-2.111	0.001*
Tumor size < 3 cm	<0.001	1.459	1.104-1.929	0.008*
Low-grade tumor	0.001	1.438	1.053-1.964	0.022*
pN_0 stage	0.004	2.512	1.019-6.195	0.045*
Tumor located in ureter	0.01	1.295	0.984-1.705	0.065
pT stage $\leq T_2$	0.023	0.907	0.639-1.287	0.982
Age more than 70	0.737			
Presence of hydronephrosis	0.065			
Smoking	0.934			
Laparoscopic surgery	0.871			
Female	0.293			
Presence of Cis	0.606			

*p<0.05, significant difference was reached

procedure. The presence of multiple tumors remains the predictive factor for IVR when patients with a history of bladder cancer are excluded. Additionally, low-grade tumors, pN_0 stage and tumor size <3cm are associated with IVR. In our previous study (7), the influence of tumor grade on bladder recurrence was not that significant when excluding the patients that died during follow-up without bladder recurrence (p=0.061). Thus, we consider this result may be attributed to the fact that high-grade, N_+ patients or those with large tumors may suffer from tumor dissemination and die prior to the detection of IVR.

With the development of medical devices, diagnostic ureteroscopy is becoming a powerful tool for patients with UTUC, and it is used to visualize and biopsy the entire upper urinary tract with a technical success approaching 95% (23). Coupled with biopsies, it provides satisfactory diagnostic accuracy (24). However, concerns have been raised that tumor implantation may result from ureteroscope manipulation and irrigation. Retrograde flow, increased urine flow rate and intraluminal pressure might lead to the shedding of tumor cells, which implant in the bladder to develop recurrences. There are only 3 previous studies on the impact of diagnostic ureteroscopy for IVR after RNU, and they do not reach a consistent conclusion (9-11). Nison et al. reported that there was intravesical recurrence 146 times, which was 28% in the URS group and 27.5% in the URS+group (not significantly different). In addition, they did not find that ureteroscopy is an independent risk factor for IVR (9). Ishikawa et al. reached the same conclusion as Nison, and the 2-year bladder recurrence-free survival rate was 60.0% in their URS+group and 58.7% in their control group (10). Luo et al., by contrast, reported that ureteroscopy was associated with an increased incidence of intravesical recurrence in patients with or without a history of bladder cancer (11). In the present study, it is possible that diagnostic ureteroscopy is an

independent predictive factor for IVR, providing evidence for the intraluminal seeding hypothesis.

The question remains whether we should use diagnostic ureteroscopy as a routine preoperative examination. The European guidelines suggest that diagnostic ureteroscopy should be performed in the preoperative assessment of any UTUC patient (8). However, diagnostic ureteroscopy may have the potential risk of future intravesical recurrence by increasing tumor cell shedding during manipulation and irrigation. We should find a balance between misdiagnosis without preoperative URS, which may result in unnecessary nephrectomy, and the potential risk of IVR after RNU.

There are several limitations of this study, including the retrospective design and data collection, which may lead to selection and recall bias. No strict criteria for preoperative ureteroscopy were established, and each surgeon independently made the decision to perform URS. In spite of these limitations, our study is still the largest single-center study in China on IVR after RNU for patients without a history of bladder cancer. Further molecular genetic studies and randomized control trials are needed to help determine the mechanism for intravesical recurrence.

CONCLUSIONS

Diagnostic ureteroscopy is independently associated with intravesical recurrence after radical nephroureterectomy. Urologists should reconsider the use of diagnostic ureteroscopy as a routine preoperative assessment. We should find a balance between misdiagnosis without preoperative URS, which may result in unnecessary nephrectomy, and the potential risk of IVR after RNU.

ABBREVIATIONS

UTUC = Upper tract urothelial carcinoma
RNU = Radical nephroureterectomy
IVR = intravesical recurrence

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CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Tumor histologic grade is the most important prognostic factor in patients with penile cancer and clinically negative lymph nodes not submitted to regional lymphadenectomy

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ABSTRACT

Introduction: The presence and extension of inguinal lymph node metastasis are the main prognostic factors in patients with penile cancer. Physical exam and image exams are not adequate to evaluate inguinal lymph nodes and many patients are submitted to non-therapeutic lymphadenectomies. However, it is known that not all patients with clinically or histologically negative inguinal lymph nodes evolve favorably.
Casuistic and Methods: the authors evaluated the clinical and pathologic characteristics of 163 patients with penile carcinoma and clinically negative inguinal lymph nodes followed for three or more years and their impact on global survival (GS) and cancer-specific survival (CSS) in the 10-year follow-up. Primary pathologic tumor stage (p=0.025) and the presence of high grade of tumor differentiation (p=0.018) were predictive of CSS. The presence of high grade tumor was an independent specific prognostic factor of death risk (RR 14.08; p=0.019).
Conclusion: high histologic grade was an independent predictive factor of specific death risk in patients with penile carcinoma and clinically negative lymph nodes followed for three or more years.

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INTRODUCTION

Penile carcinoma is rare in developed countries, and is more frequent in under developed countries. India presents 3.32 cases for every 100.000 inhabitants (1). In Brazil, it accounts for 2% of all tumors in men, reaching up to 10% in some regions (North and Northeast), and it is one of the nations with the highest incidence of this disease (2).

Penile squamous carcinoma (PSC) responds to 95% of all primary malignant tumors and the first site of dissemination corresponds to inguinal lymph nodes. Usually pelvic lymph nodes are only involved when previously inguinal lymph nodes have been affected. Hematogenic dissemination is rare and is observed in less than 10% of patients (3). Without adequate treatment, patients die in two years following diagnosis due to complications related to local growth or metastasis (4).

Presence and extension of involvement of inguinal lymph nodes are the most important prognostic factors related to survival of patients with penile cancer (5). Lymphadenectomy is the only

curative treatment, even for patients with lymph node metastasis (3, 4). However, the procedure presents high morbidity, affecting significantly quality of life of patients. Inguinal lymphadenectomy is considered therapeutic for patients with lymph node metastasis and prophylactic for those with primary tumor with at least one risk factor for lymph node involvement: stage ≥T1b and/or palpable lymph nodes following treatment with antibiotics and/or unknown follow-up.

Patients without risk factors and who are committed to treatment theoretically comprise the low risk group for inguinal metastasis and are spared from prophylactic lymphadenectomy, assuming that lymph nodes are not affected. Also, some patients are not submitted to lymphadenectomy due to different reasons.

Although it is suggested that some patients with clinically negative lymph nodes may have a better evolution than those with positive inguinal lymph nodes, the absence of lymph node metastasis is not equal to therapeutic success. Some of them may present local and regional recurrence, tumor progression and death due to cancer. We evaluated some prognostic factors for global survival (GS) and cancer-specific survival (CSS) in a historical series of patients not submitted to lymphadenectomy and that did not show lymph node metastasis in a minimum follow-up of three years. The occurrence of lymph node metastasis following that period is extremely rare (6-8).

MATERIAL AND METHODS

In order to perform the study, 163 patients with penile carcinoma and clinically negative lymph nodes followed-up for three or more years, from a data bank of 279 patients were selected. Patients were treated at the Department of Pelvic Surgery of Hospital A.C. Camargo (São Paulo - SP) from 1953 to 2012. Patients with incomplete clinical or pathological data, without adequate paraffin block available for pathological analysis, submitted to adjuvant chemo or radiotherapy, with non-epithelial carcinoma of penis and those with life expectancy due to co-morbidities inferior to 6 months were excluded.

Pathologic material of all 163 patients were reviewed by specialized pathologists (Isabela Werneck, Fernando Soares). Histologic classification was made according to subgroups described by WHO (9-11), that include twelve different histologic subtypes of penile squamous carcinoma, including the usual squamous carcinoma, basaloid, condylomatous, verrucous, papillary, sarcomatoid, adenosquamous, pseudohyperplasic, cuniculatum, pseudoglandular, condylomatous - basaloid and mixed carcinomas. Each subtype presents different morphologic and pathologic characteristics (11).

Tumors were graded according to differentiation: low grade, intermediate and high grade, using the criteria described by Velazquez et al. (2008) (12). Accordingly, tumor well differentiated were those who presented similarity to normal or hyperplasic squamous cells, different only in relation to the presence of minimal basal or parabasal atypia (Figure-1). Tumors were classified as high grade when there was presence of any grade of anaplasia. After optical magnification, those areas present low or no keratinization, elevated cytoplasm-nucleus relation, thickening of basal membrane, nuclear pleomorphism, aggregated chromatin, prominent nucleolus and numerous mitosis (Figure-2). Tumors were considered moderately differentiated when they had no criteria to be considered low or high differentiated (Figure-3) (12).

The considered variables for each patient were: age, staging according to TNM AJCC 7ed, histologic subtype, tumor differentiation grade, microscopic vascular invasion (MVI), perineural invasion (PNI) and pushing or infiltrating pattern of invasion (microscopic pattern of tumor edges) (13-16). In order to perform the specific study of histologic influence as predictive factor of survival, 12 patients from the initial 163 were excluded, since 5 were considered “evaluation not possible”, and 7 “ignored”, and 151 were considered for statistical analysis (Table 1 and Figure-2). Additionally, it was evaluated follow-up time and clinical situation at the end of the study.

IBM software Statistical Package for Social Science (SPSS) version 21 was used for statistical analysis. Distribution of clinical and

Figure - 1- Squamous cell carcinoma of low grade penile. Identifies minimum basal atypia or parabasal. Hematoxylin and eosin. 200x magnification.

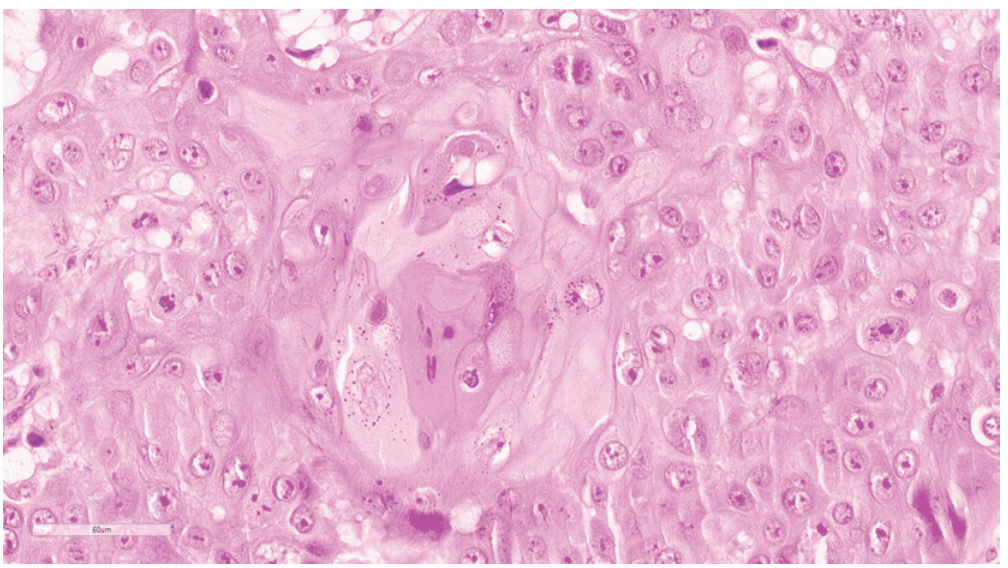
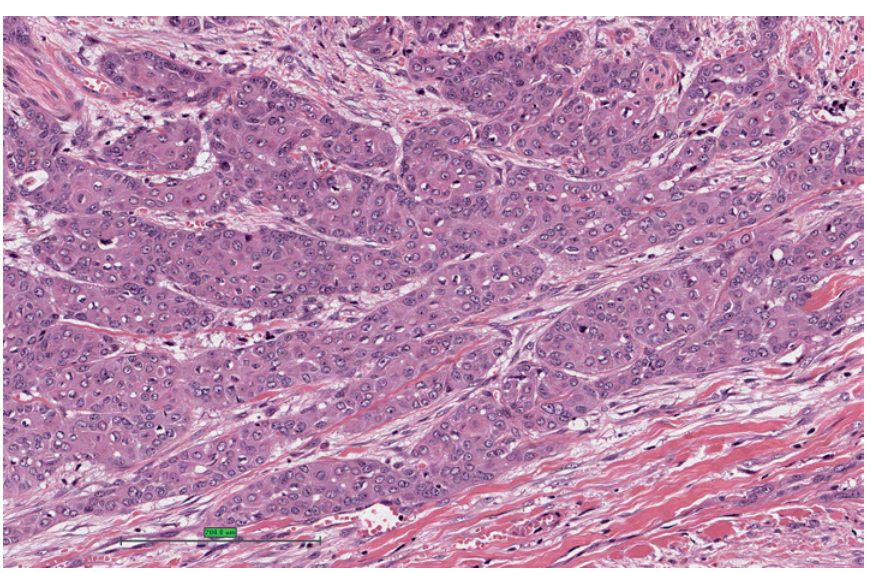


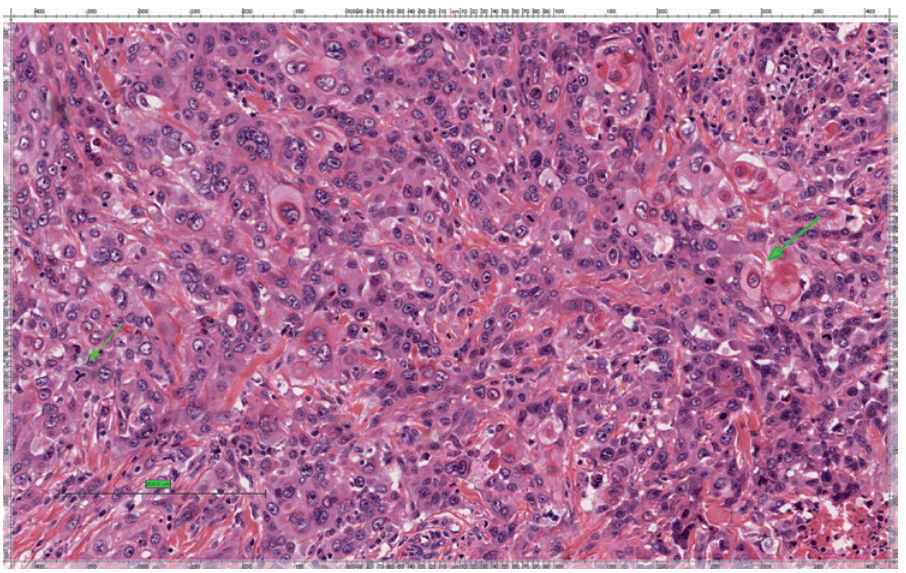
Figure - 2- Squamous cell carcinoma moderately differentiated penile. Hematoxylin and eosin.



pathologic variables was presented as contingence tables.

Identification of independent factors related to GS and CSS was performed by multiple logistic regression. Selected variables for multiple study were chosen among those who reached statistical significance at univariate analysis, as well as those who presented p values of up to 0.20. Final result of multivariate models, logistic regression and COX (1972) were obtained by stepwise forward selection: from the highest significant variable, it was added one by one every variable in an ascending order.

Figure - 3 - Squamous cell carcinoma high grade penile. dense nuclear membrane, nuclear pleomorphism, aggregated chromatin, prominent nucleoli and numerous mitoses. Hematoxylin and eosin.



In order to analyze GS and CSS it was used the Kaplan and Meier estimator (1958) in order to estimate the probability of a patient with penile carcinoma to be alive or not until the time point considered. In order to compare the estimated curves for each category of a determined variable it was used the LogRank non-parametric test. Significance level was 5%.

RESULTS

Table-1 shows the distribution of studied patients according to clinical and pathologic criteria and the impact on GS and CSS. Medium and mean follow-up were 131 and 150 months, respectively.

In relation to tumor differentiation grade, there were 66 patients with low grade tumor (43.3%), intermediate grade in 39 (25.7%) and high grade in 46 (30.9%). The most prevalent histologic type was usual squamous cell carcinoma (66.9%).

MVI and PVI were present in 11.2% and 4.5% of patients, respectively. Tumor invasion was infiltrating in 64.8% of tumors and pushing in 35.2%. There were 67 deaths (40.6%), 6 due to cancer (6.3%).

GS and CSS in 10 years of follow-up were 97.9% and 60.1% respectively. Among studied parameters, pathologic stage of primary tumor (Pt) and histologic grade influenced CSS at univariate analysis (Figure-2). Pt stage and histologic grade were selected for multivariate analysis. For that purpose, patients with intermediate grade were analyzed together with those with high grade. High grade was an independent predictive factor for GS and CSS. Patients with high grade tumor had higher probability of death due to cancer (RR 14.8; p=0.019) and global deaths (RR 1.86; p=0.023) when compared to those with low or intermediate grade (Table-2).

DISCUSSION

Squamous carcinoma of penis is a loco-regional disease with a presumable pattern of dissemination, mainly through lymphatic spread. Sequentially, it affects inguinal and pelvic lymph nodes. Presence and extension of lymph nodes metastasis determine the evolution and survival of patients, overlapping any clinical or pathologic criteria of primary tumor (19). Clinical exam fails to predict lymph node metastasis. 20% of patients with negative physical exam show micro-metastasis when submitted to inguinal lymphadenectomy. Available image exams are inaccurate for evalu-

Table 1 - Clinical and pathologic variables of 163 patients with penile carcinoma with clinically negative lymph nodes - Hospital A.C. Camargo.

Variable	N (%) SD	CSS (%)	P	GS (%)	P
Age (mean)	57 (±12.9)	-	-	-	-
Stage cN (AJCC 7th Ed.)					
cN0	98 (59.4)	98	0.216	64.3	0.174
cN1	19 (11.5)	100		52.6	
cN2	46 (27.9)	93.5		54.3	
Stage pT (AJCC 7th Ed.)					
pT1a	32 (21.2)	100		71.9	
pT1b	10 (6.6)	80		70	
pT2	81 (53.6)	97.5		58	
pT3	28 (18.5)	96.6	0.025	48.3	0.243
Histologic grade					
Low	66 (43.7)	100		63.6	
Intermediate	39 (25.8)	97.4		64.1	
High	46 (30.5)	91.3	0.018	52.2	0.078
Vascular Invasion					
Present	15 (11.2)	100		66.7	
Absent	119 (88.8)	96.6	0.526	57.1	0.908
Perineural invasion					
Present	6 (4.5)	100		83.3	
Absent	128 (95.5)	96.9	0.698	57	0.47
Invasion pattern					
Pushing	50 (35.2)	96.4		56	
Infiltrating	92 (64.8)	96	0.855	59.8	0.947
Histology					
Usual SCC	109 (66.9)	95.4		60.6	
Warty carcinoma	8 (4.9)	100		25	
Papillary carcinoma	9 (5.5)	100		88.9	
Sarcomatoid carcinoma	3 (1.8)	100		0	
Pseudoglandular carcinoma	7 (4.3)	100		57.1	
Carcinoma cuniculatum	19 (11.7)	100		63.2	
Verrucous carcinoma	1 (0.6)	100		100	
Other carcinomas	7 (4.3)	100	0.995	100	0.035
Total	163	96.9		60.1	

ation of lymph nodes with significant under-staging or over-staging (20). However, absence of lymph node metastasis is not a guarantee of therapeutic success. Factors related to primary tumor may determine different evolutions in this group of patients. Patients who present at least one risk factor for lymph node metastasis are submitted to inguinal lymphadenectomy. On the other hand, patients without any risk factors are spared of the intervention.

However, in this group of patients, some (3.1%) died due to cancer. Very few series analyze exclusively patients not submitted to inguinal lymphadenectomy. As expected, these patients not submitted to inguinal lymphadenectomy present higher rate of CSS (96.9%) and GS (60.1%) than

Table 2 - Cox regression. Analysis of GS and CSS.

Variable	CSS			GS		
	RR	95% CI	P	RR	95% CI	P
pT stage						
pT3 vs. pT1 - pT2	1.09	0.12 - 10.10	0.917	1.68	0.91 - 3.08	0.095
Histologic grade						
High vs intermediate-low	14.08	1.55 - 25.05	0.019	1.86	1.09 - 3.19	0.023

those submitted to inguinal surgery in our institution, including those with pathologic negative lymph nodes (87.1% and 52.7% respectively) (16) and those with positive lymph nodes (64.1% and no data presented, respectively) (21).

Since this was an historic series, several patients presented risk factors of inguinal metastasis: 78.7% with stage >T1a; 30.5% of high grade tumors and stages cN1 and cN2 in 39.4% but were not submitted to surgery for several reasons. It is important to have in mind that the indication of inguinal lymphadenectomy depends on the surgeon, and that referral suffered many changes in our institution throughout those six decades. In spite of that, in this group, classic prognostic parameters described such as angio-lymphatic embolization and perineural invasion were not relevant for the clinical outcome in the studied period. Histologic grade was an independent predictive factor of risk of death and death-specific. Although these high risk patients not operated have been included in the studied series, curiously CSS was very high (96.9%). Nowadays, it is not correct to not operate these patients, in view of the accumulated knowledge and several published guidelines that recommend inguinal lymphadenectomy. Still, those patients did not show inguinal recurrence following 3 years of follow-up, confirming that those were lymph node-negative. Which would be the justification for this disparity (good evolution vs adverse factors)? Maybe the explanation involves something intangible or highly subjective or the pointed clinical judgement of the physicians that decided not to perform the inguinal surgery.

Several studies confirm the negative predictive effect of histologic high grade of penile carcinoma. A retrospective review of American SEER database involving 593 patients with penile cancer and cNo stage recognized the high grade of differentiation as an independent predictive factor of death risk (RR 3.22; CI 95% (2.0-5.3)) (22). A German group (23) analyzed the role of $p16^{INK4a}$ expression as prognostic factor of penile carcinoma and additionally identified in a multivariate analysis the histologic grade (p=0.049; RR 2.47; CI 95% [1.00-6.09]) as an independent predictive factor of death due to cancer in 5 years. A Brazilian study followed up 648 patients for a median period of 11 months and observed higher CSS in 10 years among those with well differentiated tumors when compared to those with moderate differentiation or undifferentiated regardless surgical specific treatment (log rank p<0.0001 and p=0.006 respectively) (19). Different rates of 5 year-GS were observed according to tumor differentiation grade in a series of 89 patients with a median follow-up of 23 months (24). Patients with high grade tumor had lower GS in 5 years than those with moderately differentiation or low grade (53% and 29% respectively; p=0.01). At multivariate analysis, this finding was not confirmed.

Also, European Association of Urology highlight the importance of tumor differentiation grade of penile cancer. Histologic grade and primary tumor stage are the most relevant criteria for the selection of patients for inguinal lymphadenectomy (8).

The proportion of low and moderate grades has already been presented in previous studies as of minor relevance than the relative presence of high grade tumor, invariably associated with worse prognosis (25, 26). However, it is known that penile tumors are frequently heterogeneous

and may exhibit more than one grade, making histologic evaluation difficult. Also, the absence of standardized morphologic criteria for classification in different grades contributes to low reproducibility among pathologists. Graduation in differentiation extremes as performed by our group (grade 1 with very little differences in relation to normal squamous epithelium and grade 3 for tumors comprising anaplasic cells) makes classification easier and provides more consistent prognostic information. Grade 2, more susceptible to subjective interpretation depending on the pathologist, corresponds to all cases not classified as 1 or 3 (27).

In our study, pathologic evaluation of tumor was made only with hematoxylin-eosin staining. More studies are needed to validate and reproduce this high important prognostic criteria in penile carcinoma. The value of additional immune-histochemical studies for evaluation of histologic grade may be addressed by future researches.

CONCLUSIONS

In this series of patients not submitted to inguinal lymphadenectomy and that did not regionally progress after three years, a small subgroup of patients died due to cancer. Main independent prognostic factor for CSS was the presence of high grade primary tumor. Patients not operated but with high grade tumors that refuse surgery comprise a high risk group and require a more diligent follow-up.

High histologic grade remains a risk factor for death due to penile carcinoma, even in subgroups without lymph node metastasis.

LIST OF ABBREVIATIONS

SCP = squamous carcinoma of penis
Ci = confidence interval
MVI = microscopic vascular invasion
PVI = perineural invasion
RR = relative risk
CSS = cancer specific survival
GS = global survival

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Safety and efficacy of intravesical alum for intractable hemorrhagic cystitis: a contemporary evaluation

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ABSTRACT

Introduction: Hemorrhagic cystitis (HC) represents a challenging clinical entity. While various intravesical agents have been utilized in this setting, limited data exist regarding safety or efficacy. Herein, then, we evaluated the effectiveness and complications associated with intravesical alum instillation for HC in a contemporary cohort.
Materials and Methods: We identified 40 patients treated with intravesical alum for HC between 1997-2014. All patients had failed previous continuous bladder irrigation with normal saline and clot evacuation. Treatment success was defined as requiring no additional therapy beyond normal saline irrigation after alum instillation.
Results: Median patient age was 76.5 years (IQR 69, 83). Pelvic radiation was the most common etiology for HC (n=38, 95%). Alum use decreased patient's transfusion requirement, with 82% (32/39) receiving a transfusion within 30 days before alum instillation (median 4 units) versus 59% (23/39) within 30 days after completing alum (median 3 units) (p=0.05). In total, 24 patients (60%) required no additional therapy prior to hospital discharge. Moreover, at a median follow-up of 17 months (IQR 5, 38.5), 13 patients (32.5%) remained without additional treatment for HC. Adverse effects were reported in 15 patients (38%), with bladder spasms representing the most common event (14/40; 35%). No clinical evidence of clinically significant systemic absorption was detected.
Conclusion: Intravesical alum therapy is well-tolerated, with resolution of HC in approximately 60% of patients, and a durable response in approximately one-third. Given its favorable safety/efficacy profile, intravesical alum may be considered as a first-line treatment option for patients with HC.

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INTRODUCTION

Hemorrhagic cystitis (HC) refers to diffuse bleeding from the bladder, and is among the most challenging clinical entities in urology. The presentation of HC can be variable, ranging from acute life-threatening hemorrhage to a chronic indolent course. Initial management for patients with HC typically includes conservative measures such as hydration/diuresis, together with large bore 3-way Foley catheter placement, clot removal, and continuous bladder irrigation with normal saline (1-3).

For patients with persistent bleeding, various intravesical therapies have been described. One such agent utilized for HC is alum (aluminum ammonium sulfate or aluminum potassium sulfate). Alum is thought to decrease bleeding by stimulating vasoconstriction and decreasing capillary permeability (3). Nevertheless, reports to

date regarding intravesical alum instillation have consisted of small case series, largely of historical cohorts, with limited follow-up and heterogeneous definitions of success (4-11).

Herein, then, we evaluated our institutional experience with intravesical alum to determine the effectiveness and morbidity of instillation in a contemporary cohort of HC patients.

MATERIAL AND METHODS

Following Institutional Review Board approval, we identified 40 consecutive patients with HC treated with intravesical alum instillation at Mayo Clinic between 1997 and 2014. All patients were 18 years old or older and underwent intravesical instillation of 1% alum after failure of conservative measures including at least continuous bladder irrigation with normal saline and clot evacuation. Intravesical instillation of 1% alum (50gm of alum dissolved in 5 liters of sterile water) was performed at a rate of 250-300cc/hr. The duration of alum instillation was at the treating physician's discretion. Of note, serum aluminum levels were not routinely obtained during treatment.

Patient charts were reviewed for pertinent clinical and demographic variables, treatment history, length of hospitalization, adverse effects, and subsequent clinical course. Treatment success with alum was defined as no additional HC therapy following alum instillation during hospitalization other than bladder irrigation with normal saline. Of note, seven patients initiated hyperbaric oxygen therapy (HBOT) prior to completion of alum per physician preference: these patients were included in the analysis. Receipt of subsequent treatments was recorded. Duration of response was defined as the time from hospital discharge following alum instillation to subsequent hospital readmission for gross hematuria. The retrospective nature of this study precluded a standardized follow-up protocol. Readmissions were determined from chart review and included emergency room visits and inpatient readmission to our institution or elsewhere.

Continuous variables are presented as mean (SD) if they were normally distributed and as median (IQR) if not normally distributed. Categorical variables are reported as number and percentage. When testing differences between the groups, independent t test was used. For categorical variables, the $\chi 2$ test was used to compare groups. All tests were 2-sided, with $p < 0.05$ considered statistically significant. Statistical analyses were performed using the SAS software package.

RESULTS

We identified 40 patients managed with intravesical alum between 1997 and 2014 at our institution. Patient demographics are provided in Table-1. As can be seen, the most common etiology for HC was prior pelvic radiation therapy (n=38, 95%), with five patients (13%) also having received cyclophosphamide. The median time from radiation therapy was 93 months (IQR 50, 143) and the median time from cyclophosphamide therapy was 82 months (IQR 4, 157).

Prior to instillation of alum, all patients had failed continuous bladder irrigation with normal saline, and 31 (78%) had undergone clot evacuation with bladder fulguration. In addition, three (7.5%) had failed prior Amicar (one oral, one intravesical, one unknown), one patient had received prior intravesical formalin, one patient had received intravesical silver nitrate, four (10%) had undergone percutaneous nephrostomy tube placement, and one had completed a course of HBOT. In 22 patients (55%), the hospitalization during which alum was utilized represented their first admission for HC.

Alum instillation was started on median hospital day two (IQR 1, 7), and the median duration of intravesical alum instillation was 2 days (IQR 1, 2.5). Notably, five patients (12.5%) were treated for ≥5 consecutive days. Overall, alum treatment was successful (no further HC therapy prior to hospital discharge following alum, other than normal saline irrigation) in 60% of patients (24/40). Of those who did not respond, additional interventions included alternative intravesical therapies in four (silver nitrate in one, silver nitrate and formalin in one, Amicar in two) and urinary diversion in nine. Importantly, alum use decreased patient's transfusion requirement, as

Table 1 - Patient Demographics.

	Pts treated with alum N=40	Responded to Alum N= 24	Did not respond to Alum N= 16	P value
Median age, years, (IQR)	76.5 (69,83)	76.5 (70, 82)	77.5 (68, 83)	0.92*
Gender (%)				
Male	31(77.5)	17 (71)	14 (88)	0.27
Female	9 (22.5)	7 (29)	2 (12)	
Hemorrhagic cystitis etiology				
(%)	27 (67.5)	14 (58)	13 (81.25)	0.18
External beam radiation for prostate Ca				
Radiation for gynecologic Ca	6 (15)	5 (21)	1 (6.25)	0.37
Radiation for non-GU/GYN Ca	2 (5)	1 (4)	1 (6.25)	1.0
Cyclophosphamide therapy	2 (5)	1 (4)	1 (6.25)	1.0
Both Cyclophosphamide and pelvic radiation	3 (7.5)	3 (13)	-	0.26
Median BMI, kg/m^2 (IQR)	27.5 (25, 32)	28 (25, 33)	27 (24, 30)	0.4*
Diabetes mellitus (%)	6 (15%)	5 (21)	1 (6)	0.37
Hypertension (%)	29 (73%)	19 (79)	10 (63)	0.30
Coronary artery disease (%)	16 (40%)	11 (46)	5 (31)	0.51
Current or previous tobacco use (%)	13 (33%)	9 (37.5)	4 (25)	0.50
Median admission hemoglobin, gm/dL, (IQR)	9.8 (8.5,11.5)	8.95 (8.1,10.6)	10.7 (9.5,12.3)	0.04*
Median admission creatinine, mg/dL, (IQR)	1.05 (0.9,1.4)	1.0 (0.9,1.6)	1.1 (0.9,1.3)	0.68*

*independent t test. For all other variables, the $\chi 2$ test was used to compare groups.

82% (32/39) received a transfusion 30 days before alum instillation (median 4 units [IQR 3, 9]) versus 59% (23/39) receiving a transfusion in the 30 days after completing alum (median 3 units [IQR 2, 12]) (p=0.05). Not surprisingly, patients who responded to treatment were significantly less likely to receive a transfusion than non-responders (43% versus 81%; p=0.02).

Interestingly, median hemoglobin at admission was significantly lower among patients who responded to alum versus non-responders (8.95gm/dL versus 10.7gm/dL; p=0.04). No other significant differences in clinical or demographic factors were identified between patients who did versus did not respond to alum. Not surprisingly, the median number of days from cessation of alum to discharge was significantly shorter for responders versus non-responders (3 days versus 13 days; p<0.001). Additionally, in the 30 days following cessation of alum, significantly fewer of the responders required a blood transfusion than the non-responders (42% versus 81% p =0.02).

For the entire cohort the median follow-up was 16.4 months (IQR 1.9, 36.1). The median follow-up among those alive at last follow-up for alum responders was 18 months (IQR 3.5, 30) compared with 17 months (IQR 9, 52) in non-responders. Of the patients who responded to

alum, 54% (13/24) experienced a durable response, with no subsequent hospital readmissions for HC. For those with recurrent HC after an initial response to alum, 64% (n=11) of readmissions occurred within 30 days of discharge. Moreover, nearly half (5/11) of patients readmitted for HC after alum treatment subsequently underwent cystectomy for intractable HC.

Overall, alum was well tolerated, with side effects identified in 38% of patients (15/40). Adverse events included bladder spasms in 14 patients (35%), transient delirium in two patients (5%) and urinary tract infection in two patients (5%). One (2.5%) patient had an asymptomatic elevation in blood aluminum level (to 13μmol/L), after 5 days of treatment, which normalized with conservative measures. In four patients (10%), side effects prompted treatment discontinuation prior to HC resolution. Treatment was discontinued due to altered mental status (contributed to aggressive anticholinergic use) in two patients and refractory bladder spasms in two patients.

COMMENTS

We found here that intravesical alum instillation for patients with refractory HC was associated with a response rate of approximately 60%, and resulted in a decrease in patient's subsequent transfusion requirement. Approximately one-third of patients experienced a durable response to therapy, without the need for additional interventions or hospital readmission for HC. Moreover, treatment was well tolerated, with bladder spasms representing the most frequent side effect, and no clinical evidence of aluminum toxicity noted. To our knowledge, this represents the largest reported series to date on the use of intravesical alum for refractory hemorrhagic cystitis (4-11).

Management of HC remains a challenging clinical entity due to the often persistent nature of bleeding, as well as the significant comorbidities inherent to the afflicted patient population. At the same time, there is a lack of current consensus regarding the optimal management strategy for these patients. Initial conservative measures include hydration, continuous bladder irrigation with normal saline, as well as cystoscopy with clot evacuation (1, 2, 12). Failing these, however, treatment options include various intravesical agents such as formalin, silver nitrate, Amicar and alum.

Alum is an astringent that causes protein precipitation in the interstitial spaces and cell membrane when used intravesically (1, 3). This leads to extracellular matrix contraction, decreased capillary permeability, vasoconstriction, and sclerosis of exposed capillary endothelium (3, 13). Alum is formed with dissolution of aluminum ammonium sulphate or aluminum potassium sulphate in sterile water to make a 1% alum solution (50gm of alum dissolved in 5 liters of sterile water) (1-3, 12).

Ostroff and Chenault first described intravesical alum irrigations in 1982, with the successful treatment of six patients with hemorrhage (4). Since this initial report, several albeit small case series have reported response rates ranging from 50-100% (4-11). Indeed, Arrizabalaga et al., in what is to our knowledge the largest prior reported series of alum treatment, described the outcomes of 15 patients who received intravesical alum, with a complete response in 66%, partial response in 15%, and failure in 20% (5). Likewise, a small prospective randomized study (of intravesical alum versus prostaglandin) noted that 66% of patients treated with alum (6/9) had completed cessation of hemorrhage (6). Several other series, all with ≤12 patients, have demonstrated initial success rates for alum instillation ranging from 50-100% (7-11). We found a similar response rate (60%), while on longer-term follow-up approximately one-third of patients remained free from readmission for HC at a median of 17 months after receiving alum. Thus, use of alum may help stabilize patients and delay or potentially avoid more invasive therapies with increased morbidity, such as cystectomy with urinary diversion (14).

With regard to the morbidity associated with alum instillation, our data is consistent with reports to date that have suggested that local symptoms such as bladder spasms represent the most common adverse effect of treatment (1, 5, 11). Bladder spasms were typically managed

with anticholinergic therapy, and did not require treatment cessation in most cases. While systemic alum absorption and resulting neurotoxicity have been cited as a concern with alum instillation, this is a rare event in patients with normal renal function, as the kidney rapidly excretes serum aluminum and toxicity is uncommon (1, 3, 13). In fact, alum causes decreased capillary permeability and causes vasoconstriction, which likely helps limit systemic absorption. Notably, no cases of clinical evidence for aluminum toxicity were identified here.

Importantly, all patients in our series had adequate renal function to permit treatment, and as such we did not routinely monitor serum aluminum levels. One patient who had received five days of intravesical alum was assessed and found to have an elevated serum aluminum level (13ng/mL), but remained asymptomatic. Alum therapy was stopped regardless and his serum level subsequently returned to normal. Meanwhile, two separate patients developed delirium, which was attributed to aggressive anti-cholinergic therapy for bladder spasms (an aluminum level was checked in one patient and was normal). Regardless, alum therapy was stopped (along with anti-cholinergic medications), and the delirium resolved.

We recognize that our study is limited by its retrospective design. Indeed, given the highly variable presentation of patients with HC, and the limited randomized trial evidence for guidelines, management remains at the discretion of the treating physician. Likewise, a number of patients had received treatments for HC prior to alum use and their impact on outcomes is unclear. In addition, as a tertiary referral center, specific details about patient care prior to referral/transfer were unavailable in some cases. As well, we must acknowledge patients readmitted locally without contacting with us may not have been captured. Lastly, while this series represents the largest cohort reported to date regarding the use of alum in treating HC, the sample size is nevertheless limited. Additional studies, ideally in a prospective clinical trial are needed to define the optimal management strategy for patients with HC.

CONCLUSIONS

Intravesical alum instillation is associated with minimal morbidity and results in resolution of bleeding in approximately 60% of patients. Approximately one-third of patients maintain a durable response to treatment. Given its favorable safety/efficacy profile, intravesical alum should thereby be considered a first-line treatment option for patients with HC.

ABBREVIATIONS

HC = hemorrhagic cystitis
HBOT = hyperbaric oxygen therapy

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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A large 15 – year database analysis on the influence of age, gender, race, obesity and income on hospitalization rates due to stone disease

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ABSTRACT

Purpose: To assess the public hospitalization rate due to stone disease in a large developing nation for a 15-year period and its association with socio-demographic data.
Materials and Methods: A retrospective database analysis of hospitalization rates in the Brazilian public health system was performed, searching for records with a diagnosis code of renal/ureteral calculi at admission between 1998-2012. Patients managed in an outpatient basis or private care were excluded. Socio-demographic data was attained and a temporal trend analysis was performed.
Results: The number of stone-related hospitalizations increased from 15.7%, although the population-adjusted hospitalization rate remained constant in 0.04%. Male:female proportion among hospitalized patients was stable (49.3%:50.7% in 1998; 49.2%:50.8% in 2012), though there was a significant reduction in the prevalence of male hospitalizations (-3.8%;p=0.041). In 2012, 38% of hospitalized patients due to stone disease had 40-59 years-old. The ≥80 years-old strata showed the most significant decrease (-43.44%;p=0.022), followed by the 20-39 (-23.17%;p<0.001) and 0-19 years-old cohorts (-16.73%;p=0.012). Overall, the lowest relative hospitalization rates were found for yellow and indigenous individuals. The number of overweight/obese individuals increased significantly (+20.6%), accompanied by a +43.6% augment in the per capita income. A significant correlation was found only between income and obesity (R=0.64;p=0.017).
Conclusions: The prevalence of stone disease requiring hospitalization in Brazil remains stable, with a balanced proportion between males and females. There is trend for decreased hospitalization rates of male, <40 and ≥80 years-old individuals. Obesity and income have a more pronounced correlation with each other than with stone *disease*.

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INTRODUCTION

Urinary stone disease is a common disorder, which distresses the economically active population. In the United States of America (USA), urolithiasis was reported to affect 1.116 per 100.000 18 to 64-year-old employees covered by two large insurance carriers in the year 2000 (1-4).

Kidney stones are not usually quiescent and typically cause patients considerable pain,

ultimately leading to hospitalization. International epidemiological data suggest that the incidence and prevalence of stone disease are increasing (1-4). The probability of developing kidney stones varies according to numerous factors including age, gender, race, geographic location and body mass index (BMI). In addition, a change in the gender and age distribution of stone formers over time has been described, with an increasing participation of females and older individuals (5-7). This highlights the importance of better understanding current regional hospitalization rates in order to work on stone prevention and treatment strategies. Unfortunately, current population-based data on the frequency of kidney stone episodes in Latin nations are limited and studies describing recent national time trends are lacking.

The goals of the present study are to assess the rate of hospitalizations due to upper urinary tract calculi in Brazil over the past 15 years and to evaluate the influence of gender, age, race, income, obesity and geographic residence on urolithiasis trends.

MATERIALS AND METHODS

National Background

Brazil comprises a 8.5 billion-km2 area. According to Brazilian Institute of Geography and Statistics (Instituto Brasileiro de Geografia e Estatística-IBGE), the national population has reached more than 200 million people in 2014 (9). The Public Health System of Brazil, named Sistema Único de Saúde (SUS), supposedly provides health coverage for all citizens of the country. Recent data has shown approximately 47%-74% of residents truly uses resources from SUS and not from private care (10).

Study Design and Data Source

A retrospective, population-based, cross--sectional time series analysis was performed using data derived from an administrative database of the Brazilian Public Health System (SUS).

Public Health System has a longitudinal hospital inpatient database (Sistema de Informação Hospitalar-SIH/SUS), which contains records from discharges for all cities and regions of the country (11). Each discharge includes up to five inpatient diagnoses per hospitalization. All diagnoses are coded using the International Classification of Disease (9th revision, ICD-9 until December 1997; 10th revision, ICD-10 since January 1998). Patient and socio-demographic characteristics included are gender, race, age, ZIP code of residence, and income.

The Consumer Expenditure Survey (Pesquisa de Orçamento Familiar-POF), the demographic census, and the national research by household sample (Pesquisa Nacional por Amostra de Domicílios-PNAD), all conducted by IBGE, aims to portray the Brazilian Population. Body mass index (BMI) data of the Brazilian population was extracted from the POF, which has been performed in two periods: 2002-2003 and 2008-2009. Income per capita data was extracted from PNAD and the demographic census, the latest one being performed in 2010 (12).

Database Analysis

Hospital discharges between January 1st/1998 and December 31st/2012 were abstracted from the SIH/SUS. In 2012, Public Health System hospitals had around 326 thousand beds. All inpatient hospitalizations in the 15-year period for patients of any age with a primary or secondary diagnosis code of N20.x (calculus of kidney or ureter) were abstracted. Only patients with ureteral or renal stones were considered in the analysis.

The absolute number of inpatient hospitalizations due to stone disease per year was analyzed nationally and also separately for the five distinguish regions of the country, named South, Southeast, Midwest, North, and Northeast regions. Absolute numbers were also adjusted for local population to provide a prevalence perspective. Patients managed in an outpatient basis or those from private care were not considered in the analysis.

Demographics were summarized for the entire cohort of patients. The specific demographics included were age, gender, race, income and obesity. For population comparison, prevalence estimates were adjusted by direct standardization to the Census population. Age was reported divided in five strata (0-19; 20-39; 40-59; 60-79; and

≥80 years-old). Income was reported as national and regional income per capita per year. In regards to BMI, individuals were divided into 2 groups: normal if BMI<25Kg/m^2; overweight and obese if BMI≥25Kg/m^2).

Statistical analysis

Statistical analysis was performed using SPSS V.19 (Chicago, IL). Qualitative variables were presented as absolute numbers and relative frequencies at each time point. Percent variation from study beginning to end was also contemplated. Quantitative variables were analyzed in terms of temporal trends: prevalence trends over the 15-year period were quantified by the estimated annual percent change (EAPC) using the least squares linear regression methodology (13). The linear regression model considered a 95% confidence interval with a regression coefficient. A Spearman's correlation test was performed to seek for associations between hospitalization rate, obesity, and income. Significance level was p<0.05.

RESULTS

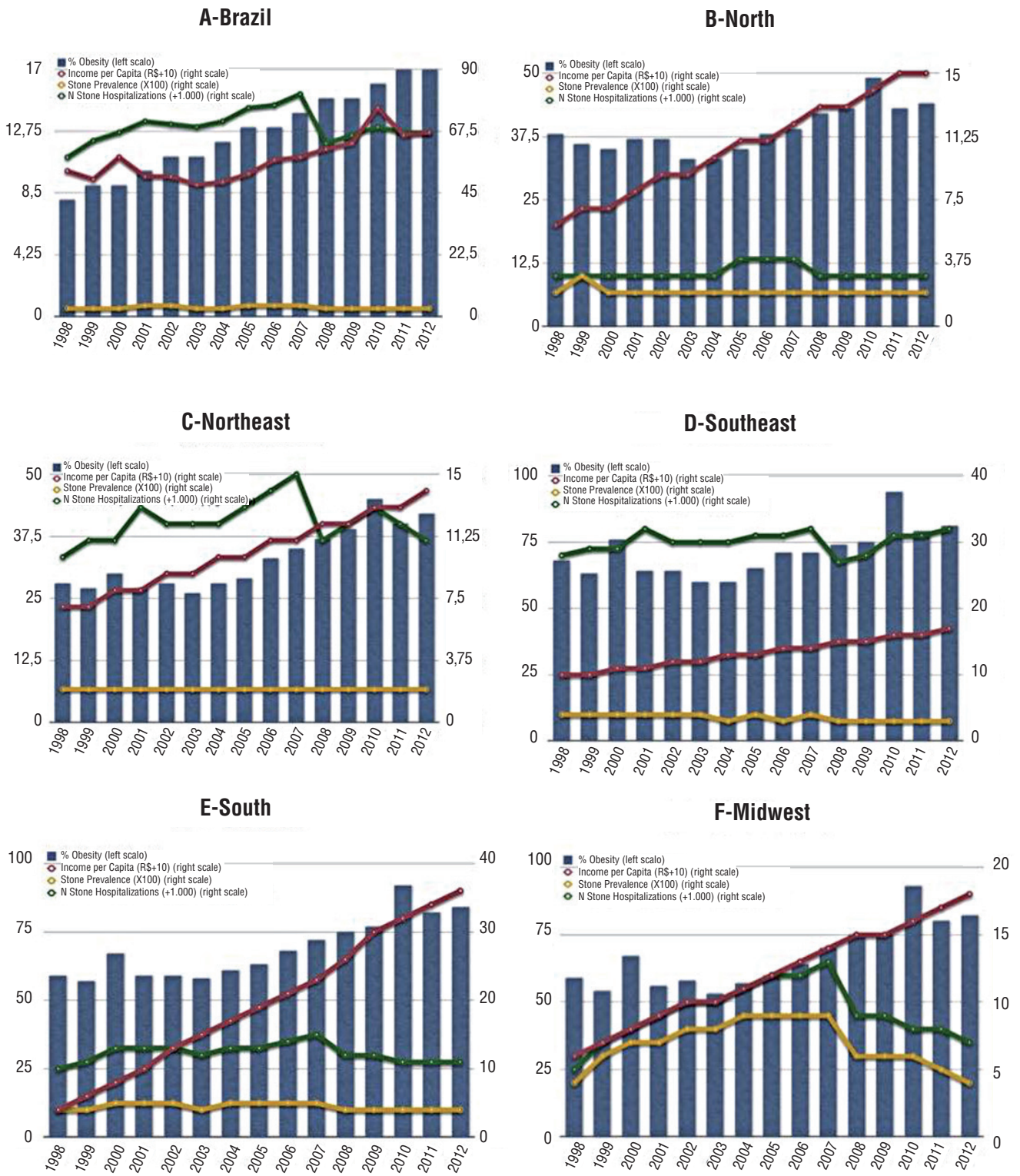
Hospitalization Trends

The absolute number of stone-related hospitalizations increased from 58165 in 1998 to 67306 in 2012, accounting for a 15.7% increase in Brazil. However, the prevalence of hospitalizations adjusted for the Brazilian population remained constant in 0.04% (Table-1; Figure-1A). All regions presented a non-significant increase in the absolute number of hospitalizations (Table-1A), which was not sustained when adjusted for the local population (Table-1B).

Table 1 - Temporal trends for absolute number (A) and prevalence (B) (adjusted to the population x 100.000 people) of stone-related hospitalizations in Brazil and all five regions between 1998 and 2012.

A	N (1998)	N (2012)	% Variation	EAPC [95% CI]	p-value
Brazil	58165	67306	+ 15.7%	294.7 [-454.9; 1044.3]	0.411
Male	28675	33090	+ 15.4%	0.000% [-0.001; 0.002]	0.707
Female	29490	34216	+ 26.2%	0.000% [-0.002; 0.001]	0.707
Regions					
North	3281	3715	+ 13.2%	18.3 [-27.8; 64.4]	0.407
Northeast	10454	11991	+ 14.7%	109.1 [- 51.4; 269.7]	0.166
Southeast	28532	32521	+ 14.0%	95.7 [-104.9; 296.3]	0.321
South	10780	11942	+ 10.8%	-13.1 [-178.4; 152.3]	0.867
Midwest	5118	7137	+ 39.4%	84.6 [-216.1; 385.3]	0.554
B	**(1998)**	**(2012)**	**% Variation**	**EAPC [95% CI]**	**p-value**
Brazil	35.9	34.7	- 3.5%	-0.32 [-0.67; 0.04]	0.078
Male	35.9	34.8	- 3.0%	-0.0003% [-0.0006; 0.000]	**0.041**
Female	35.9	34.6	- 3.8%	-0.0003% [-0.0008; 0.0001]	0.123
Regions					
North	27.6	22.7	- 17.80%	- 0.44 [-0.73; -0.16]	**0.005**
Northeast	22.8	22.2	- 2.52%	- 0.07 [-0.37; 0.23]	0.628
Southeast	41.3	39.8	- 3.63%	- 0.35 [-0.60; -0.11]	**0.009**
South	44.6	43.1	- 3.51%	- 0.52 [-1.05; 0.02]	0.057
Midwest	46.5	49.5	+ 6.30%	- 0.54 [-2.81; 1.74]	0.618

Figure 1 - Number and Proportion of Hospitalizations in Brazil and all five regions, with % of obesity and Income Analysis.



The Midwest region had the highest hospitalization prevalence (0.05% in 1998 and 2012) and the highest progression rate, although non--significant (+6.2%; p=0.61; Figure-1F). The Northeast region showed the lowest hospitalization rate (0.02% in 1998 and 2012), which remained stable (-2.5%; p=0.62; Figure-1C). The only two regions with a significant change in time trends for hospitalization rates were the North (-17.8%; p=0.005) and the Southeast region (-3.63%; p=0.009), both with significant decreases (Table-1B).

Gender Analysis

Male:female proportion among hospitalized patients was relatively stable in Brazil, with 49.3%:50.7% in 1998 and 49.2%:50.8% in 2012 (Figure-2A). The increase in the absolute number of hospitalizations for men (+15.4%) and women (26.2%) showed no significant estimated annual percent change (p non-significant) (Table--1A). However, there was a significant reduction in the prevalence of male hospitalizations in the analyzed period (-3.8%; p=0.041) (Table-1B).

Age Temporal Changes

In 2012, the prevalence of hospitalizations due to stone disease in the Brazilian population stratified by population age was 7.1% from 0-19 years; 39.6% 20-39 years; 38.0% 40-59 years; 13.7% 60-79 years; and 1.5% ≥80 years (Figure-2B).

In absolute numbers, both 0-19 and 20-39 years-old strata presented a significant decrease with a negative EAPC (p<0.001), while 40-79 years-old individuals had a significant increase (p<0.001) (Table-2A). In discordance, all age strata showed a decrease in the prevalence of stone-related hospitalization rates between 1998 and 2012. However, temporal trend analysis revealed a stable situation for the 40-59 (-3.06%; p=0.06) and 60-79 years--old groups (-9.26%; p=0.087). The ≥80 years--old strata showed the most significant decrease (-43.44%; p=0.022), followed by the 20-39 years-old (-23.17%; p<0.001) and 0-19 years--old cohorts (-16.73%; p=0.012) (Table-2B).

Ethnicity Evaluation

There were no records of hospitalization by race until 2009 and no time-trend analysis could be performed. The distribution by race in 2012 was 43.4% white; 2.2% black; 22.1% brown; 0.5% yellow; 0.03% indigenous and 31.8% with no information (Figure-2C).

In 2012, the distribution by race showed two patterns: in the North, Northeast and Midwest regions, brown citizens were the most common among those hospitalized due to stone disease (55.8%, 35.2%, 32.1%, respectively). In the Southeast and South regions, there was a predominance of Caucasians (54.1% and 76.9%, respectively). There were high percentages of missing records (no information) in all regions. Overall, the lowest relative hospitalization rates were found for yellow and indigenous individuals (Figure-2C).

Obesity, Income and Hospitalization Correlation

The number of overweight and obese individuals increased significantly (+20.6%) (Table--3A) and was accompanied by a +43.61% augment in the per capita income (Table-3B). The correlation of hospitalization rate with income (R=-0.36; p=0.22) and obesity rate (R=-0.42; p=0.11) was not significant. Conversely, a positive significant correlation was found between income and obesity (R=0.64; p=0.017) (Figure-1). Table-3 shows overweight prevalence and income per capita for Brazil and all five regions.

The North region showed the highest increase in the proportion of overweight people (+32.8%; 35.0% in 2003 and 46.5% in 2009) and the lowest increase on income per capita (+27.8%; US$199.29 in 1998 and US$152.67 in 2010) (Table-3). Surprisingly, there was a decrease in the incidence of hospitalization by stone disease (-17.8%; p=0.005) (Table-1B).

In Northeast region, there was an increase in relative number of overweight people (+22.5%; 35.5% in 2003 and 43.5% in 2009) and also in the income per capita (+58.4%; US$89.22 in 1998 and US$141.31 in 2010) (Table-3). Hospitalization remained stable (-2.52%; p=0.628) (Table-1B).

The Southeast region showed stability of hospitalization rates (-3.63%; p=0.009) (Table-1B), with an increase in the number of

Figure 2 - Gender (A) and Age (B) distribution among patients hospitalized due to stone disease in Brazil from 1998 to 2012; Ethnicity (C) distribution of hospitalizations for different Brazilian regions in 2012.

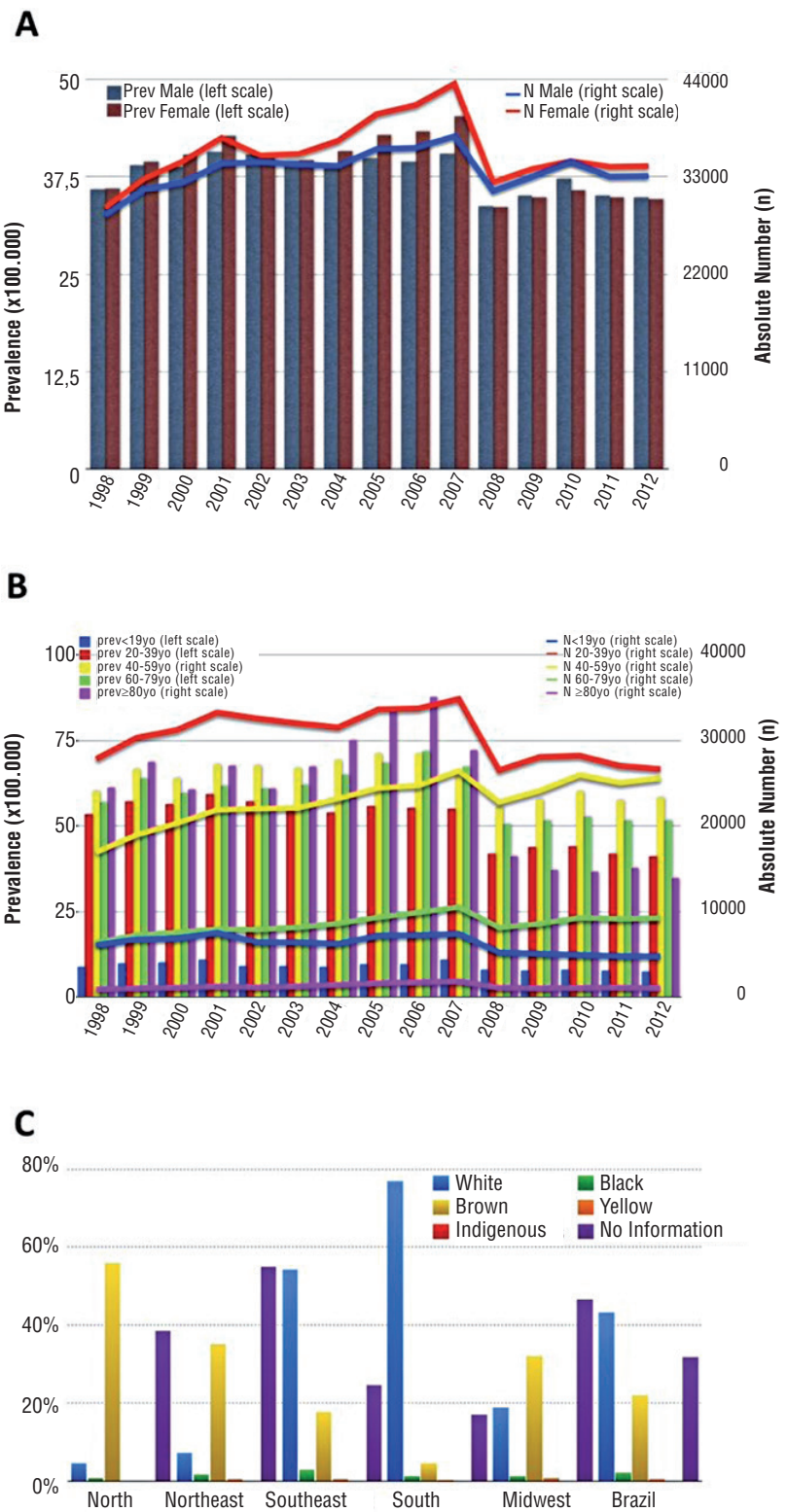


Table 2 – Temporal trends for absolute number (A) and prevalence (B) (adjusted to the population x 100.000 people) of stone-related hospitalizations in Brazil between 1998 and 2012 according to age strata.

A	(1998)	(2012)	% Variation	EAPC [95% CI]	p-value
Brazil					
0 to 19 years	6089	4757	- 21.87%	-0,26% [-0,32;0,11]	<0.001
20 to 39 years	27856	26671	- 4.25%	-0,60% [-0,65;-0,55]	<0.001
40 to 59 years	16933	25607	+ 51.2%	0,65% [0,53;0,76]	<0.001
60 to 79 years	6349	9240	+ 45.5%	0,21% [0,18;0,24]	<0.001
≥ 80 years	938	1031	+ 9.91%	0,01% [-0,34;0,35]	0.976
B	(1998)	(2012)	% Variation	EAPC [95% CI]	p-value
Brazil					
0 to 19 years	8.9	7.4	- 16.73%	-0.16 [-0.28;-0.04]	**0.012**
20 to 39 years	53.3	41	- 23.17%	-0.12 [-1.75;-0.70]	**<0.001**
40 to 59 years	60.1	58.2	- 3.06%	-0.59 [-1.20;0.03]	0.060
60 to 79 years	56.8	51.6	- 9.26%	-0.71 [-1.54;0.12]	0.087
≥ 80 years	61.3	34.6	- 43.44%	-2.33 [-4.27;-0.39]	**0.022**

Table 3 – Temporal variation of overweight prevalence (A) and income per capita (B) in Brazil.

A			
People overweight	% (2003)	% (2012)	% Variation
Brazil	40.2 %	48.5%	+ 20.6%
Regions			
North	35.0%	46.5%	+ 32.8%
Northeast	35.5%	43.5%	+ 22.5%
Southeast	42.2%	49.0%	+ 16.1%
South	44.6%	52.3%	+ 17.3%
Midwest	39.9%	47.5%	+ 19.0%
B			
Income per capita	US$ (1998)	US$ (2010)	% Variation
Brazil	164.72	237.00	+ 43.6%
Regions			
North	119.29	152.67	+ 27.8%
Northeast	89.22	141.31	+ 58.4%
Southeast	210.73	291.05	+ 38.2%
South	184.16	283.82	+ 54.2%
Midwest	182.54	288.41	+ 58.2%

overweight individuals (+16.1%; 42.2% in 2003 and 49.0% in 2009) and in the income per capita (+38.2%; US$210.73 in 1998 and US$291.05 in 2010) (Table-3).

In the South region, there was a relative increase in total number of overweight people (+17.3%; 44.6% in 2003 and 52.3% in 2009) and in the income per capita (+54.2%; US$184.16 in 1998 and US$283.82 in 2010; Table-3), with stable rates oh hospitalization (-3.51%; p=0.057) (Table-1B).

In the Midwest region, there was a relative increase in the number of overweight citizens (+19.0%; 39.9% in 2003 and 47.5% in 2009) and in the income per capita (+58.2%; US$182.54 in 1998 and US$288.41 in 2010; Table-3). In parallel, hospitalization increased (+6.3%; p=0.618) (Table-1B).

DISCUSSION

The importance of prevention is highlighted in an era of stone disease prevalence growth worldwide. Factors that may play a role in the increasing risk of kidney stone disease include sunlight and heat, dietary consumption of animal protein, salt and water, and certain clinical conditions like obesity. After mapping the present scenario, better policies and actions might be commenced to improve prevention. However, a standardized analysis of hospitalizations due to stone disease has never been made in Brazil. Our study tries to somehow depict the national scenario.

A number of studies have shown that the lifetime prevalence of kidney stones among adults increased significantly in the past years. The National Health and Nutrition Examination Survey showed a significant 37% increase in the prevalence of stone disease in the American population between 1976-1980 and 1988-1994 (1). Benjamin et al. used the Hospital Episode Statistics (HES) to evaluate national trends in the UK between 2000 and 2010 and found similar trends, the number of upper urinary tract stone hospital episodes increased by 63% (4). In the other hand, Ghani et al. studied the US Nationwide Inpatient Sample in the period of 1999-2009 and found that the total number of hospitalizations for upper urinary tract calculi was found relatively stable (181 592 in 1999 vs. 190 040 in 2009, EAPC 0.07%, P=0.83, 95% CI: -0.53-0.68%) (6). Importantly, their research does not account for patients treated in an outpatient basis, a common practice in the USA.

In the period studied (1998-2012), the absolute number of inpatient stone-related episodes increased 15.7% in Brazil (14). However, the prevalence of hospitalizations remained almost stable. This is in disagreement with the world literature (1-4). Possible explanations could rely in the fact that in an economic growth scenario, more people are gaining access to private care treatment and not using the public health system. In addiction, a combined analysis of stone disease treatment including inpatient and ambulatory cases could show different results. Unfortunately, we do not have in Brazil a comprehensive private and outpatient database to address this matter.

The prevalence of stone disease increases with age and is relatively uncommon before 20 years-old. However, the incidence increases rapidly and peaks from ages 40 to 60 years and then decreases from ages 65 years and thereafter (2). We found that all age strata presented a significant decrease in hospitalization prevalence, with the exception of 40-59 and 60-79 years-old populations. In other words, while young individuals are less hospitalized, older ones have stable rates of hospitalization. This could be a result of the direct or indirect influence of obesity, metabolic syndrome and diabetes mellitus.

Physiologically, obesity has been linked to increased renal excretion of calcium and uric acid, as well as increased urine acidity, all of which increase the risk of stone formation. Presuming obesity as a marker for the metabolic syndrome, which is linked epidemiologically and physiologically to risk of kidney stones, we investigated potential associations between obesity and a history of kidney stones. We found a significant increase in overweight and obese individuals in the studied period (+20.6%). A previous study preformed by Taylor et al. determined that body size is independently associated with the development of kidney stones (15). The authors showed a relative risk of kidney stones in obese men to be 1.33 vs that in normal weight men, whereas in obese women the

risk was up to 2.09 times higher than in normal weight women. In their study, body mass, weight gain in adulthood, and waist circumference were associated with an increased risk of incident stones. Women were at a higher risk for stone disease than men for all of these risk factors. In our investigation, a significant correlation was only found between stone episodes and income per capita. No association between obesity and stone disease prevalence could be found. Again, the analysis of private care could alter these findings.

Historically, men have been more likely to develop urinary calculi with an incidence and prevalence of up to 2–4 times greater than that for women (16, 17). In the present study, women and men had similar proportion in regards to hospitalization due to upper urinary tract calculi. In accordance to literature data, although we found a non-significant increase in the absolute number of male (+15.4%) and female (+26.2%) hospitalizations, there was a significant reduction in the prevalence of male hospitalization rates (-3.8%; p=0.041). Scales et al. showed that the ratio of males to females treated as inpatients for stone disease changed from 1.7:1 in 1997 to 1.3:1 in 2002 (5). Based on self-reports of stone disease, Stamatelou et al. showed a larger increase in women rates than in men between 1976 and 1994 (1).

Mean average temperature is believed to be a major contributor to variation in geographic risk for stone disease, since higher average temperatures and greater sun exposure could result in oversaturation of stone-forming salts in the urine. In our study, however, the sunnier and heater regions (North and Northeast) showed the lowest hospitalization rates. Those two regions are also the poorer regions of the country and this finding could reflect the difficulty in access to health coverage. The most developed regions of Brazil (South, Southeast) showed the highest hospitalization rates due to stone disease. In addition, individuals living in developed areas have a different lifestyle of people living in underdeveloped areas and they tend to feed on processed food and to be more sedentary. Thus, the explanation for the geographic variation in kidney stone risk is probably multifactorial in our country.

Potential limitations to our study must be stressed. SIH/SUS is a snapshot of a patient's admission and the study does not distinguish patients who may have had multiple admissions for the same or a new calculus episode. Patients discharged from the emergency room, those undergoing outpatient treatments or those who are managed in the supplementary system are not captured. Also, the database used does not distinguish elective from emergency hospitalizations and the accuracy of coding for procedures is unclear. Between 1998 and 2012, extra corporeal shock-wave lithotripsy had a significant relative increase (+338%) what may have lead to a decrease of number of hospitalization, since SWL can be performed in and outpatient basis (14). Another drawback was that in 2008 a new form of register for hospitalizations was implemented, leading to a potential coding bias. Lastly, the nature of the dataset does not allow the true capturing of risk factors and we can only hypothesize on causality. Importantly, this is not a phenomenon exclusive of Brazil. Our analysis included all inpatient hospitalizations for stone disease performed in SUS in the analyzed period and provided an accurate picture of local and regional stone disease tendencies.

CONCLUSIONS

The prevalence of stone disease requiring hospitalization in Brazil remains stable, with a balanced proportion between males and females. There is trend for decreased hospitalization rates of male, <40 and ≥80 years-old individuals. Obesity and income have a more pronounced correlation with each other than with stone disease.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Ultrasound - guided access during percutaneous nephrolithotomy: entering desired calyx with appropriate entry site and angle

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ABSTRACT

Objectives: To evaluate the success of ultrasonography directed renal access in entering the target calyx from proper entry site and in the direction of renal pelvis during percutaneous nephrolithotomy (PCNL).
Materials and Methods: PCNL cases who were operated on by one fellow from May-June 2014 were included in this study. A vertically placed ultrasound probe on the patient flank in prone position was used to identify the preselected target calyx. Needle was advanced through needle holder and fluoroscopy was used to document the entered calyx, site and angle of entry.
Results: Successful entering to the target calyx was achieved in 43 cases (91%). Successful entry with appropriate entry site and angle was observed in 34 cases (72%). Reasons for failure were minimal hydronephrosis, upper pole access and high lying kidneys.
Conclusions: Although it is feasible to access a preselected calyx by ultrasonography guidance during PCNL, but entry to the calyx from the appropriate site and direction is another problem and needs more experience. In cases of minimal hydronephrosis, superior pole access or high lying kidneys, ultrasonography is less successful and should be used with care.

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INTRODUCTION

Percutaneous nephrolithotomy (PCNL) is now the treatment of choice for surgical management of large renal stones. Fluoroscopy has traditionally been the method for obtaining access to the pelvicalyceal system. Later ultrasonography access to the pelvicalyceal system has been introduced and popularised by some researchers (1-8). It has previously been shown that ultrasonography guided PCNL is equivalent to or even sometimes better than fluoroscopy guided PCNL in terms of stone free rate (1, 5, 9), operation duration (5), bleeding (5, 9) and complications (5).

A perfect percutaneous access tract to the pelvicalyceal system should be made through the tip of renal papilla in the targeted calyx and to be along the axis of renal calyx (10) so that the guide wire is passed into the pelvis and/or ureter. In fluoroscopy guided PCNL, entry to the targeted calyx

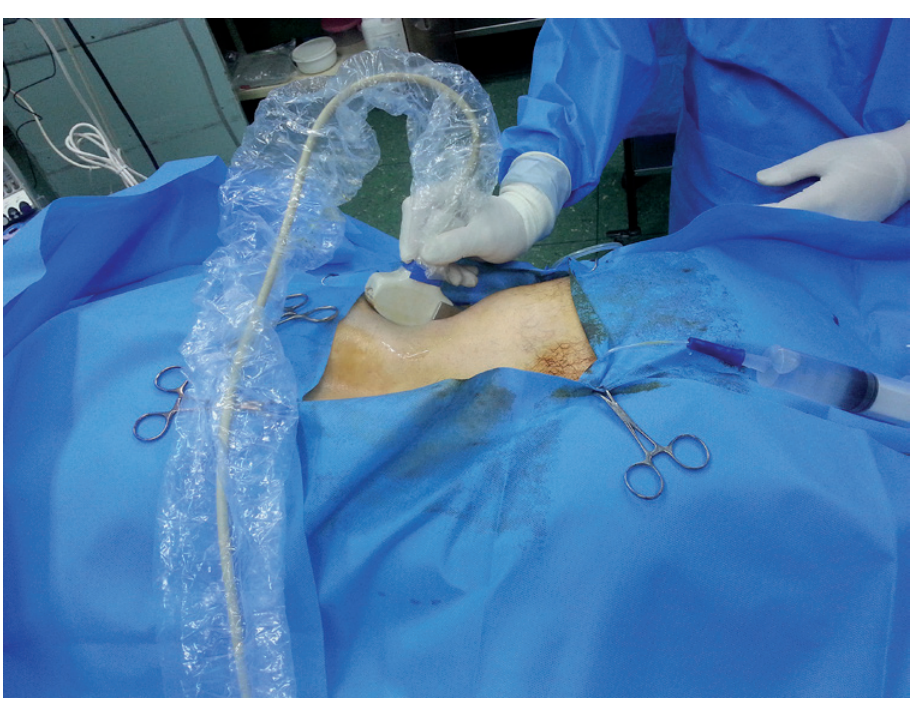
is evident by 2 directional fluoroscopy images. There is a concern with ultrasonography guided PCNL for entry into the previously selected calyx especially for urologists who are not familiar with ultrasonography. We could not find any publication evaluating the precision of ultrasonography in targeting the desired calyx in the desired direction and through renal papillae.

The aim of this study was to access the effectiveness of ultrasonography guided PCNL renal access in entering the targeted calyx and in the direction of renal pelvis.

MATERIALS AND METHODS

Patients who were candidate for PCNL in Labbafinejad Hospital and were operated by one fellow during May-June 2014 were included. PCNL cases included patients with large renal stones (>2cm) or patients with renal stones >1.5cm in horseshoe kidneys. No specific exclusion criteria were applied and typical cases for PCNL within the study period were included. The operating fellow had prior experience in fluoroscopy guided PCNL (>400 cases) and in ultrasonography guided PCNL (>50 cases). PCNL was done according to the standard protocol described before (3). In brief, cystoscopy was done in lithotomy position and a 4-6F ureteral catheter was inserted. Then the patient was turned into prone position. Ultrasonography was done by Siui Apogee 3800 (Guangdong, China) ultrasonography machine. A convex abdominal probe was placed on the flank of the patient parallel to the long axis of the kidney so that the 2D view included all possible calices from superior to inferior poles (Figure-1). The calyx which had been selected for access based on preoperative imaging (IVP or CT scan) was identified by ultrasonography. Then an 18Y gauge Shiba needle was advanced through a needle holder attached to the side of the ultrasonography probe. Entering the target calyx was confirmed by viewing the needle path on the ultrasonography monitor. Then the needle obturator was removed and saline was infused through the ureteral catheter. The outflow of urine from the needle proved the presence of the needle in the pelvicalyceal system. The guide wire was passed through the needle into the PC system until resistance was felt. Then radio-opaque contrast was injected through ureteral catheter and

Figure 1 - Ultrasonography probe was hold on the back of the patient parallel to the long axis of the kidney.



after opacifying the pelvicalyceal system, needle path and guide wire route were documented by fluoroscopy (Figure-2). If the entered calyx was different or not appropriate for PCNL or the calyx was entered from positions other than the papillae, the needle and guide wire were withdrawn and access was obtained under fluoroscopy guidance. The use of fluoroscopy here was as to confirm the accuracy of ultrasonography guided access and not as an adjuvant to ultrasonography guided access. In patients whom the obtained access was judged wrong and not feasible for safe PCNL by fluoroscopic images, a second access was obtained by means of fluoroscopy and the ultrasonography taken access was considered as failed.

In this study proper entry site into renal calyx was defined as entry from the surface of renal papillae and not from the lateral walls of the calyx or any other entry sites. Proper entry direction was defined as the direction or angle that leads to renal pelvis (Figure-3). Tract was dilated by guidance of fluoroscopy/ultrasonography and PCNL was performed by pneumatic lithoclast and stone fragments were removed by forceps.

Placement of nephrostomy or removal of ureteral catheter was done according to the judgement of the attending surgeons.

The ethics of this study was approved by the local committee institutional board review. All patients were informed about the study and informed consent obtained.

RESULTS

52 patients were enrolled during the study period. 5 patients were excluded from the study and their data is not presented in the below sections. Reasons for exclusion from the study were: fat body resulting in poor ultrasonic view of the kidney (1 patient), ectopic kidney with poor ultrasonic view (1 patient), high lying kidneys with poor longitudinal ultrasonic view because of rib shadows or stones in superior calices making ultrasonic view of the stone by ultrasonic probe in longitudinal view difficult (3 cases).

Details of the 47 remaining patients and their operations have been outlined in Table-1. As explained in the methods section, access phase

Figure 2 - Documentation of guide wire entry site and angle by fluoroscopy after injecting contrast media from ureteral catheter. In this case guide wire was passed from proper entry site and coiled in renal pelvis

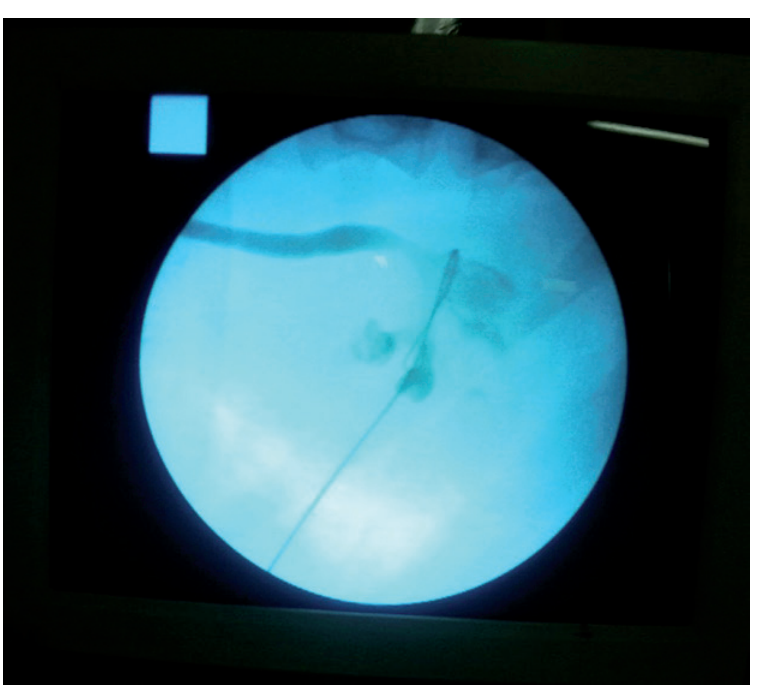
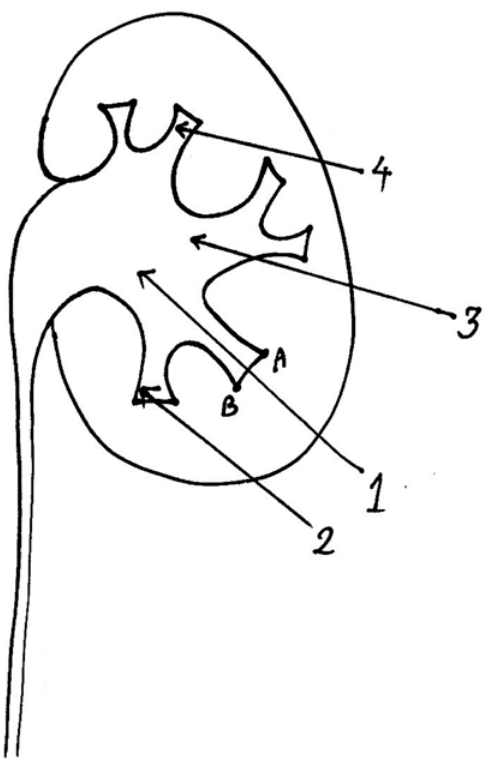


Figure 3 - Definition of proper entry site and angle in this study. Proper entry site was defined as the surface of renal papillae (from point A to point B). Proper entry angle was defined as an angle that leads to renal pelvis (parallel to the axis of entered renal calyx).



was totally guided by ultrasonography in all patients. Tract dilation was ultrasonography guided in 7 patients and with fluoroscopy guidance in 40 patients. No case of bowel injury or solid organ injury was observed in the studied patients. Successful entry into targeted calyx was observed in 43 cases (91%). Successful entry, proper entry site and appropriate direction (all) were observed in 34 cases (72%). In cases with proper entered calyx (n=43), appropriate entry site and coiling of guide wire were observed in 38 and 39 cases (88% and 91% respectively).

Table-2 compares the factors affecting false entered calyx. The percent of falsely entered calices increases steadily from 4% to 50% when the accessed calices changes from lower calices to upper calices (Table-2). False entered calices were observed in 17% of patients with nil-minimal hydronephrosis compared to 0% in patients with moderate or severe hydronephrosis. If hydronephrosis is recategorized into nil--minimal versus moderate-severe (2 categories) then the observed differences are statistically significant (fisher p-value=0.049). Age, side of operation, gender, history of open stone surgery or PCNL and stone location were not associated with false entered calices.

Table 1 - Patients' demographic data and operations' characteristics.

Variable*	
Age, years	46.9±12.6
Gender, Male/Female	34/13
Positive Hx of PCNL	17 (36)
Positive Hx of OSS	6 (13)
Side, Left/Right	30/17
Access, L/Mid/U	25/20/2
Hydronephrosis, N/Mod/S	23/17/7
Stone location, U/Mid/L/P/Mul/Stag	2/2/12/13/10/8
Operation duration, minutes	55.3±21.7
Transfusion	1 (2)
Stone free rate	41 (87)

Hx = History; **PCNL** = Percutaneous nephrolithotomy; **OSS** = Open stone surgery; **L** = Lower pole; Mid = Middle pole; **U** = Upper pole; **N** = Nil-minimal; **Mod** = Moderate; **S** = Severe; **P** = Pelvis; **Mul** = Multiple stone locations; **Stag** = Staghorn
* Data is presented as mean±SD, N(%) or N/N

Table-3 compares factors influencing proper entry site and coiling of calyx in patients in whom the entered calyx was right (N=43). False entry site was observed in the only patient with upper pole access to the upper pole stone. (We excluded 3 patients with upper-middle pole stones in whom rib shadows precluded good longitudinal view of the kidney by ultrasonography probe). The percent of false entry site constantly decreased from 16% in nil-minimal hydronephrosis to 0% in severe hydronephrosis, however this difference was not statistically significant. False entry site was more often observed on the right side PCNLs (p=0.04). Failure of the guide wire to coil in calyx/pelvis was not associated with any studied variables. Failure to coil was observed in 3 patients (16%) with nil-minimal hydronephrosis, no case with moderate hydronephrosis and

Table 2 - The association of false entered calyx with studied variables.

Factors†		Wrong entered calyx		P-Value
		Yes	No	
Age, years		54.7±10.3	46.0±12.2	0.17
Access	Lower pole	1(4)	24(96)	0.10*
	Middle pole	2(10)	18(90)	
	Upper pole	1(50)	1(50)	
Side	Right	2(12)	15(88)	0.61
	Left	2(7)	28(93)	
Hydronephrosis	Nil-Minimal	4(17)	19(83)	0.06*
	Moderate	0(0)	17(100)	
	Severe	0(0)	7(100)	
Gender	Male	2(6)	32(94)	0.30
	Female	2(15)	11(85)	
Hx of OSS	Yes	1(17)	5(83)	0.43
	No	3(7)	38(93)	
Hx of PCNL	Yes	1(6)	16(94)	1.0
	No	3(10)	27(90)	
Stone location	Upper pole	1(50)	1(50)	0.14
	Middle pole	0(0)	2(100)	
	Lower pole	0(0)	12(100)	
	Pelvis	1(8)	12(92)	
	Multiple sites	2(20)	8(80)	
	Staghorn	0(0)	8(100)	

OSS = Open stone surgery; **PCNL** = Percutaneous nephrolithotomy
***** Chi square p-value for linear by linear association
† Data are presented as mean±SD or N (%)

1 case with severe hydronephrosis (Table-3). The patient with severe hydronephrosis in whom the guide wire failed to coil was a 53 years old male with staghorn left kidney stone that occupied the whole pelvis and most renal calices leaving little free space for guide wire to coil or move freely in the calyx.

DISCUSSION

A perfect access for PCNL should pass from the papillae into the collecting system and direction of the needle path should be coincident with the long axis of the target calyx (11). There have been reports about the safety and success of ultrasonography directed renal access or solo-sono PCNL (1-6, 12). Nevertheless, we could neither find any article describing the success of ultrasonography in targeting the access to the pre-selected calyx nor we could find publications describing the situations regarding renal anatomy or stone morphology that make ultrasonography directed renal PCNL difficult or bothersome.

In this study, we observed a high success rate for entering targeted calyx by ultrasonography guided renal access. Reasons for failure were: 1) minimal/no hydronephrosis in the target calyx. The absence of hydronephrosis makes identifica-

Table 3 - The associations of false entry site or failure of guide wire to coil with studied variables.

Factors†		False entry site		P-value	Failure to coil		P-value
		Yes	No		Yes	No	
Age, years		45.4±13.6	46.1±12.2	0.90	55.5±2.4	45.0±12.4	0.10
Access	Upper pole	1(100)	0(0)	0.12	0(0)	1(100)	0.12
	Middle pole	2(11)	16(89)		2(11)	16(89)	
	Lower pole	2(8)	22(92)		2(8)	22(92)	
Side	Right	4(27)	11(73)	0.04	3(20)	12(80)	
	Left	1(4)	27(96)		1(4)	27(96)	0.11
Hydronephrosis	Nil-Minimal	3(16)	16(84)	0.83	3(16)	16(84)	0.26
	Moderate	2(12)	15(88)		0(0)	17(100)	
	Severe	0(0)	7(100)		1(14)	6(86)	
Gender	Male	4(12)	28(88)	1.0	3(9)	29(91)	1.0
	Female	1(9)	10(91)		1(9)	10(91)	
Hx of OSS	Yes	2(40)	3(60)	0.09	0(0)	5(100)	1.0
	No	3(8)	35(92)		4(11)	34(89)	
Hx of PCNL	Yes	3(19)	13(81)	0.34	2(12)	14(88)	0.62
	No	2(7)	25(93)		2(7)	25(93)	
Stone location	Upper pole	1(100)	0(0)	0.29	0(0)	1(100)	0.55
	Middle pole	0(0)	2(100)		0(0)	2(100)	
	Lower pole	1(8)	11(92)		1(8)	11(92)	
	Pelvis	2(17)	10(83)		0(0)	12(100)	
	Multiple*	1(12)	7(88)		1(12)	7(88)	
	Staghorn	0(0)	8(100)		2(25)	6(75)	

OSS = Open stone surgery; **PCNL** = Percutaneous nephrolithotomy
***** Multiple stone locations
† Data are presented as mean±SD or N(%)

tion of the stone and its surrounding calyx difficult on ultrasonography especially by less experienced urology surgeons. We usually inject normal saline through ureteral catheter in patients with nil-minimal hydronephrosis to augment the magnitude of hydronephrosis during the access phase of the operation. Another alternative can be injection of diuretic agents before the access phase so that the access time is roughly in the peak action duration of the diuretic agent 2). Failure to enter the preselected calyx was less often observed in lower calices in comparison with middle to upper calices. Therefore, in difficult or borderline cases, selection of lower calyx for entry especially in equivocal cases may be associated with a higher success rate. As illustrated in the methods section, appropriate entry site in this study was defined as the convex area of the tip of the calyx

and not its lateral walls (Figure-3). Reasons for false entry site were: 1) Stones in superior calices. To avoid shadows of ribs, we placed the ultrasonography probe beneath the rib cage. As a result, the angle of the needle, its path length and the visibility of the stone were more difficult when the stone was in the superior calices. Also, the path of the needle is from near the inferior pole of the kidney toward its superior pole. Then it seems imperative that the entry to the superior calyx will be from its lateral walls not from the convex surface of its papillae (Figure-3). To overcome such a problem, it is possible to place the ultrasonography probe transversely on the patient flank instead of placing it vertically and perform the access beneath the ribs or even from the window between the ribs. This was not included in the study protocol and it is possible that the identification of the target calyx in relation to other calices would be more difficult on a transverse plan. Our personal experience is that it is possible to perform intercostal access by ultrasonography guidance when ultrasonography probe is placed transversely between ribs. In this method, the target calyx can be selected by cephalic-caudal movement of ultrasonography probe. However, more experience is required due to rib shadows and narrow entry space on skin 2). High lying kidneys. The same points and problems described for superior pole stones are also pertinent to high lying kidneys. After experiencing false entry site in the patient with superior pole stone, we excluded high lying kidneys when the ultrasonography view of the whole kidney was not possible because of rib shadows.

In univariate analysis, right side PCNLs were associated with more frequent false entry sites (Table-3). After performing a multivariable logistic regression analysis, the association of laterality was no longer statistically significant when hydronephrosis and accessed calyx were included in the equation.

In order to use ultrasonography for taking access in PCNL, there should be a clear view of the kidney calices on ultrasonography monitor. In situations in which this image is not clear, the success of ultrasonography in properly targeting the access calyx, its entry site or entry angle can be impaired. In our limited experience, this scenario happened in the following situations 1). A very fat patient with normal lying kidney with a 2cm stone in the lower calyx, 2) One muscular patient with body mass index of 27 with low lying mal-rotated kidney with a pelvis stone, 3) Three patients with stones in middle or upper kidney calices so that when the ultrasonography probe was placed longitudinally beneath the ribs, the view of the whole kidney or the segment containing the stone was not clear. In a few cases we tried to overcome this problem by angling the ultrasonography probe end caudally and pressing it on the patient back below the ribs but in these cases, this simple manoeuver could not solve the problem. Nevertheless, in such cases it is possible to obtain access to lower calyx without the need to observe the calices containing stones on ultrasonography monitor and then perform PCNL. In the protocol of the current study, we requested to have the image of kidney calices and containing stones which was not possible in the above cases but just for the sake of performing PCNL, it is enough to obtain ultrasonography guided access through a lower calyx and then perform PCNL by rigid or flexible nephroscope. Having mentioned these solutions, we think it is still safer to have fluoroscopy equipment at hand in such cases in case of failed ultrasonography guided access.

We do acknowledge the operator dependency of ultrasonography a limitation of the results of this study. The experience of the operator can influence the obtained results. Nevertheless, there has been a publication by Japtag et al. in which the guidance of access by fluoroscopy versus ultrasonography yielded similar outcomes in hands of a trainee urologist with little prior experience in PCNL (13). It is necessary here to emphasize that fluoroscopy was not used in this study as an adjuvant to ultrasonography for accessing the kidney but ONLY to verify the access taken by the surgeon. In cases that the access was judged wrong by fluoroscopic images, a second access was taken by means of fluoroscopy and the ultrasonography access was considered as failed and analysed accordingly.

CONCLUSIONS

Although it is feasible to access a preselected calyx by ultrasonography guidance during PCNL, but entry to the calyx from the appropriate site and direction is another problem and needs more experience. In patients with minimal hydronephrosis, upper pole access or high lying kidneys this success rate is lower or the entry site into the calyx is less perfect. In such cases, it is advisable to have fluoroscopy equipment at hand.

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CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Is there a difference between presence of single stone and multiple stones in flexible ureterorenoscopy and laser lithotripsy for renal stone burden <300mm² ?

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ABSTRACT

In this study, we aim to evaluate and compare the effectiveness of flexible ureterorenoscopy (f-URS) for solitary and multiple renal stones with <300 mm² stone burden. Patients' charts who treated with f-URS for kidney stone between January 2010 and June 2015 were reviewed, retrospectively. Patients with solitary kidney stones (n:111) were enrolled in group 1. We selected 111 patients with multiple kidney stones to serve as the control group and the patients were matched at a 1:1 ratio with respect to the patient's age, gender, body mass index and stone burden. Additionally, patients with multiple stones were divided into two groups according to the presence or abscence of lower pole stones. Stone free status was accepted as complete stone clearence and presence of residual fragments < 2 mm. According to the study design; age, stone burden, body mass index were comparable between groups. The mean operation time was longer in group 2 (p= 0.229). However, the mean fluoroscopy screening time in group 1 and in group 2 was 2.1±1.7 and 2.6±1.5 min, respectively and significantly longer in patients with multiple renal stones (P=0.043). The stone-free status was significantly higher in patients with solitary renal stones after a single session procedure (p=0.02). After third month follow up, overall success rate was 92.7% in Group 1 and 86.4% in Group 2. Our study revealed that F-URS achieved better stone free status in solitary renal stones <300 mm². However, outcomes of F-URS were acceptable in patients with multiple stones.

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INTRODUCTION

Recently, Shock Wave Lithotripsy (SWL) is recommended as one of the first line treatment modalities for renal stones under 300mm² stone burden, according to European Urology Association Guidelines (1). Although, SWL has high success rates and higher patient compliance, effectiveness of SWL tends to decrease in lower pole stone(s), hard stone(s) such as calcium oxalate monohydrate stones and multiple stones (2). On the other hand, percutaneous nephrolithotomy (PNL) has favourable results for renal stone(s) regardless of stone type, but procedure has potential serious complications including bleeding necessitating transfusion, septicaemia and colonic injury (3). Additionally, multiple stones may require multiple accesses which may increase the number of complications.

With advancements in endoscopic technology and increasing surgical experience, flexible ureterorenoscopy (f-URS) has become an

important treatment modality for renal stones(s). Modern flexible ureterorenoscopes may access all pelvicaliecal system including lower pole, and Holmium Laser provides effective stone fragmentation regardless of stone type. Additionally, use of ureteral access sheath facilitate the passage of stone fragments, which improves patients quality of life after the procedure (4). Many authors had achieved up to 90% stone free rates with acceptable complications in f-URS procedure in moderate sized stones (5, 6).

Although there are many studies showing the effectiveness of f-URS for solitary renal stones, studies evaluating the effectiveness of f-URS in multiple renal stones is limited. In this study, we aimed to evaluate and compare the efficacy and safety of f-URS for solitary and multiple renal stones with <300mm^2 stone burden. To our knowledge, this is the first study comparing the effectiveness of f-URS for solitary and multiple renal stones.

MATERIALS AND METHODS

In a single tertiary academic center, 413 patient's charts who were treated with f-URS for kidney stone between January 2010 and June 2015 were reviewed, retrospectively. However, patients datas were recorded prospectively. Patients who had kidney stone burden <300mm^2 were enrolled into the study. Stone burden was calculated according to European Association of Urology guideline's formula (1). Patients with a solitary kidney stone and multiple kidney stones were divided as group 1 and group 2, respectively. At the end of our evaluation, 111 patients enrolled in group 1. We selected 111 patients with multiple kidney stones to serve as the control group and the patients were matched at a 1:1 ratio with respect to the patient's age, gender, presence of solitary kidney and stone burden. Patients under 18 years of age and patients with renal abnormalities were excluded from the study. Additionally, to evaluate the effect of lower pole stone on f-URS outcomes, patients with multiple stones were divided into two groups according to the presence or absence of lower pole stones.

In all patients, detailed medical history was obtained and physical examination was performed. Preoperatively, renal stone and kidney characteristics were assessed by intravenous urography (IVU) and/or computed tomography (CT). Patients demographic parameters including sex, age, body mass index (BMI), degree of hydronephrosis, stone size, stone number and location were recorded. Hemoglobin measurements, serum creatinine level, platelet counts and coagulation screen tests were assessed preoperatively. All patients had sterile urine culture prior to procedure. Finally, all patients signed an informed consent form before surgery.

f-URS technique

In all cases, a standardized f-URS procedure was performed by well-trained surgeons. After induction of general anesthesia, semirigid ureteroscopy was performed for visual assessment of ureter and facilitate the placing of ureteral access sheath. 8.7F digital flexible ureteroscope (DUR-D Gyrus ACMI, Southborough, MA, USA) or a 7.5F fiber-optic (Storz FLEX-X 2, Tuttlingen, Germany) with a 200 or 273µm laser fiber were used for treatment. Stone fragmentation was performed with holmium laser with an energy of 0.8 – 1.5J and a rate of 5 – 10Hz. Stone fragments <2mm were left for spontaneous passage and basket retrieval was performed for >2mm stone fragments. At the end of each procedure, semi-rigid ureteroscopy was performed to check the integrity of the ureter and a 4.8F double-J catheter was routinely placed in each patient. Operation time was accepted as the time passed from insertion of the flexible ureterorenoscope to the completion of double-J catheter placement. Our patients were discharged from the hospital on first postoperative day. In the 3rd week of operation, double-J catheter was removed. Additional procedures were recommended to our patients if residual stone fragments bigger than 4mm were identified.

Initial postoperative stone-free status was evaluated at hospital discharge with a kidney – ureter – bladder radiogram. In follow-up, stone-free rates were determined in an outpatient clinic setting at 3 months postoperatively with low-dose spiral CT. Stone free status was accepted as complete stone clearence and presence of residual fragments less than 2mm.

During statistical analyses values were evaluated as numbers, means, percentages and

intervals. Numbers and percentages were compared using Chi-square test. Before the comparison of means of values, the values were evaluated for homogenity. Homogenously distributed values were compared using Student T test and heterogenously distributed values were compared using Mann Whitney U test.

RESULTS

According to the study design, gender, age, BMI and stone burden were similar between two groups (p=1, p=0.924, p=0.592, p=0.936, respectively). Additionally, degree of hydronephrosis, stone opacity and presence of solitary kidney were comparable between groups (p=0.363, p0.065=, p=0.531, respectively). The mean stone number was 2.38 in Group 2. Preoperative parameters are summarized in Table-1.

The percentage of different scope type usage (fiberoptic or digital) were similar between groups (p=0.299). Although the mean operation time was longer in group 2, there was no statistically significant difference (p=0.229). However, the mean fluoroscopy screening time in group 1 and in group 2 was 2.1±1.7 and 2.6±1.5 min, respectively and significantly longer in patients with multiple renal stones (P=0.043). Stone relocation from lower pole to the pelvis or to another appropriate calyx was performed in 68.8% of our

Table 1 - Pre-Operative Characteristics.

	Single stone	Multiple stones	P value
Number	111	111	
Mean age (years)	46.1±14.1	45.9±13.9	0.924
Mean body mass index (kg/m^2)	26.6±4.5	26.3±5.2	0.592
Mean stone area(mm^2)	155.3±45.2	155.9±60.2	0.936
Gender			1
Male	55.9%	55.9%	
Female	44.1%	44.1%	
Operation side			0.351
Left	51.5%	53.2%	
Right	49.5%	46.8%	
The mean stone number			<0.001
	1	2,38	
Hydronephrosis			0.363
0	37	28	
1	43	41	
2	22	35	
3	7	6	
4	1	1	
Solitary Kidney	6.4%	4.5%	0.531
Stone opacity			0.065
Opaque	100	106	
Non opaque	11	5	
Previous SWL history	45%	53.2%	0.314

SWL = Shock Wave Lithotripsy

patients. The mean hospitalization time of our patients were 20.6±14.5 and 22.5±16.8 in group 1 and group 2, respectively.

The complications were graded according to the Clavien-Dindo classification (7). Although complication rates were slightly higher in group 2, the difference was not statistically significant. Post operative severe pain was the most common unfortunate event that was seen in 14 (12.6%) and 16 (14.4%) patients in group 1 and group 2, respectively. Post-operative fever requiring the change of antibiotic therapy was seen in 5 patients of group 2. Severe bleeding that resolved spontaneously in follow-up occured in one patient in group 1 and in two patients of group 2. None of our patients required blood transfusion. Double-J catheter migration occurred in five patients (2 patients in group 1 and 3 patients in group 2). The double-J catheter was inserted under local anesthesia in two patients and under general anesthesia in three patients, respectively (Figure-1).

The stone-free status was significantly higher in patients with solitary renal stones when compared to patients with multiple renal stones (89.2% vs. 83.8%) after a single procedure (p=0.02). A second f-URS was required for 3 patients in group 2. These patients were completely stone free. After three months of follow-up, overall success rate was 92.7% in group 1 and 86.4% in group 2 (Table-2). Additionally, stone compositions are listed in Table-2.

In group 2, 92 patients with lower pole stone and 19 patients without lower pole stone were categorized in group 2a and in group 2b, respectively. Demographic characteristics were well-matched between groups (Table-3). Also, mean operation time and mean fluoroscopy screening time was similar (p=0.431 and p=0.436, respectively). Complication rates were not signifi-

Figure 1 - Comparison of post operative stone free status and complications between patients with single stone and multiple stones.

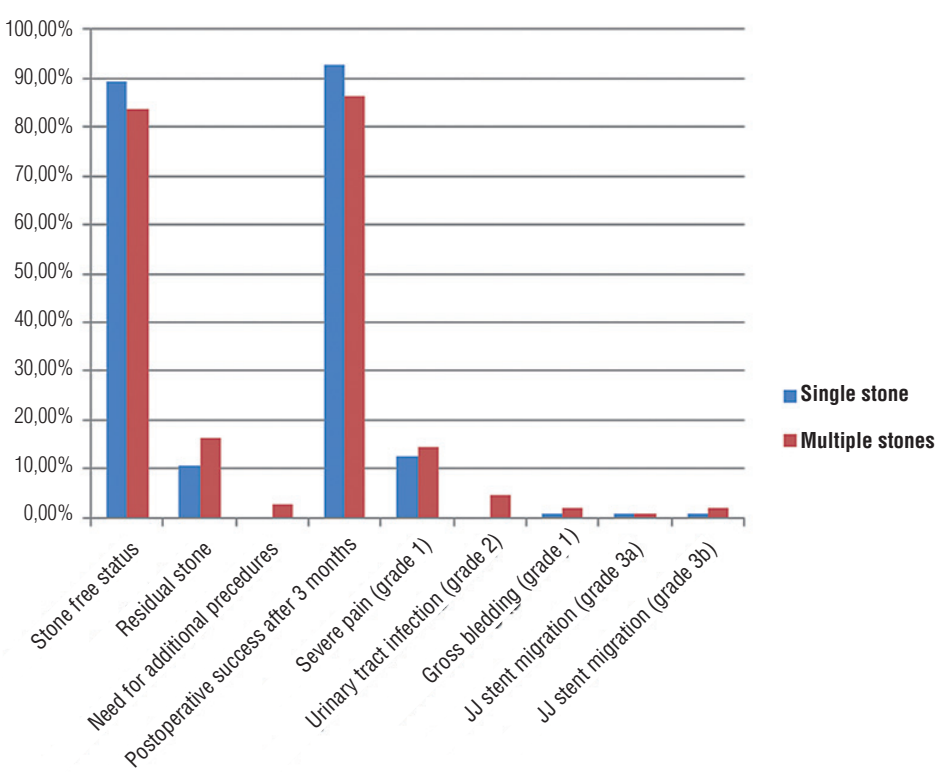


Table 2 - Operative and post-operative characteristics.

	Single stone	Multiple stones	P value
Number	111	111	
Type of f-URS			0.299
Flex-X2 (Fiberoptic)	94	87	
Dur-D (Digital)	17	24	
Mean operation time(minutes)	44.6±16.8	47.8±22.2	0.229
Mean fluoroscopy time(minutes)	2.1±1.7	2.6±1.5	0.043
Mean hospitalisation time(hours)	20.6±14.5	22.5±16.8	0.387
Post operative complications			0.282
Severe pain (grade 1)	14 (12.6%)	16 (14.4%)	
Need for antibiotic change due to fever (grade 2)	0%	5(4.5%)	
Gross bleeding (grade 1)	1(0.9%)	2(1.8%)	
JJ Catheter migration (grade 3a)	1(0.9%)	1 (0.9%)	
JJ Catheter migration (grade 3b)	1 (0.9%)	2 (1.8%)	
Postoperative success after single session			0.020
Stone free status	99 (89.2%)	93(83.8%)	
Residual stone	12(10.8%)	18(16.2%)	
Need for additional procedures	0%	3(2.70%)	0.385
Postoperative success after 3 months	103 (92.7%)	97 (86.4%)	0.016
Stone analysis			0.865
Calcium oxalate monohydrate	28	37	
Calcium oxalate dihydrate	11	15	
Uric acid	4	2	
Cystine	4	7	
Struvite	1	2	
Mixt	8	13	

JJ catheter = Double-J catheter

cantly different between groups (p=0.616). Stone free status was 87.0% in group 2a and 84.2% in group 2b after a single procedure (p=0.856) Figure-2). Second look f-URS was performed in two patients and one patient in group 2a and in group 2b, respectively (Table-4).

DISCUSSION

The treatment recommendation for kidney stone(s) in urolithiasis guidelines substantially depends on stone burden and location of the stone. However, many studies had demonstrated stone number's effect on the success and complications of the treatment modality, especially in SWL. We believe that number of stones can effect the decision of treatment modality and this variable should be added in urolithiasis guideline's recommendations. Thus, we investigate the efficiency of f-URS in multiple stones, where SWL is recommended as the first line treatment option, according to stone size.

Table 3 - Pre-Operative characteristics of patients with multiple renal stones according to absence/presence of lower pole stone.

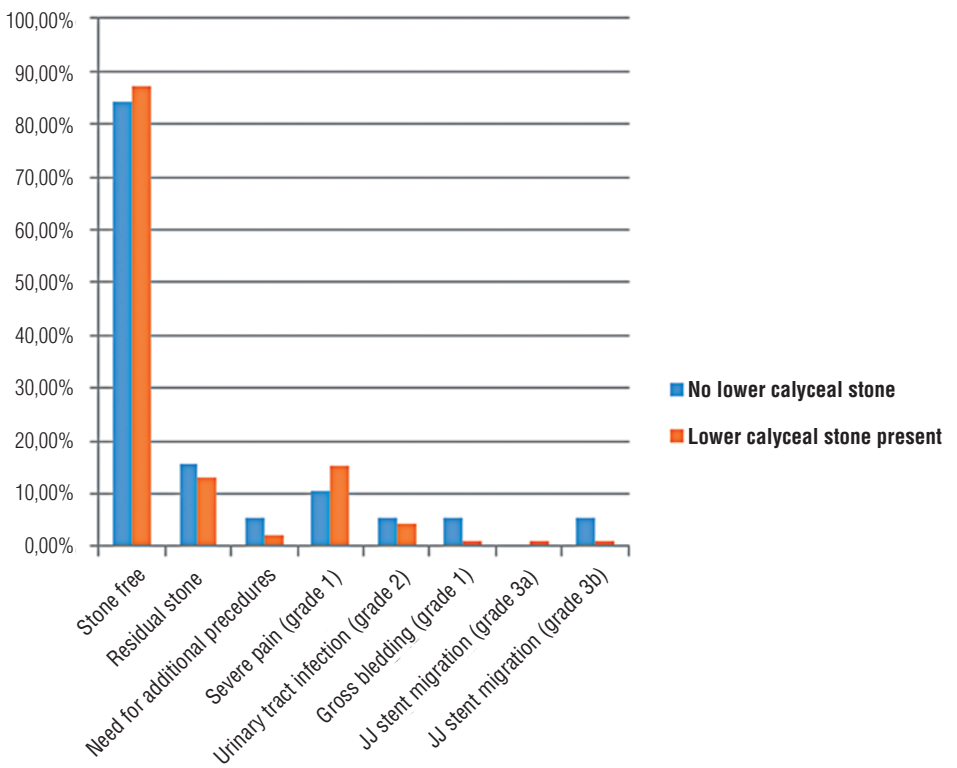
	Lower calyceal stone present	No lower calyceal stone	P value
Number	92	19	
Mean age (years)	45.8±13.9	46.6±14	0.803
Mean body mass index (kg/m^2)	26.7±5.5	24.3±2.4	0.075
Mean stone area(mm^2)	156.4±60	153.3±63.1	0.839
Gender			0.086
Male	26.3%	73.7%	
Female	47.8%	52.2%	
Operation side			0.211
Left	54.3%	31.6%	
Right	45.7%	68.4%	
Stone localisation			<0.001
Multiple stones with lower pole stone	92	0	
Multiple stones without lower pole stone	0	19	
Hydronephrosis			0.218
0	23	5	
1	36	5	
2	28	7	
3	5	1	
4	0	1	
Solitary Kidney	5.4%	0%	0.298
Stone opacity			0.352
Opaque	87	19	
Non opaque	5	0	
Previous SWL history	54.3%	47.4%	

SWL = Shock Wave Lithotripsy

The efficacy and safety of SWL on single kidney stone under 300mm^2 is well described, however, success rate of the procedure declines as the number of stones increase. Cash et al. reported ≤50% stone free rate after SWL, in the treatment of multiple intrarenal stones (8). McAdams et al. performed SWL in 149 patients and 32 of them had multiple renal stones. The mean number of stones was 1.87 in successfully treated patients and 2.81 in those with treatment failure, in their study (p=0.065) (9). In addition, stone free rates decrease below 70% for single renal stone located in the lower pole (10). Thus, we believe SWL is not a suitable option for multiple renal stones, especially if one or more stone(s) are located in the lower pole.

Percutaneous nephrolithotomy is another treatment alternative for renal stone(s) under 300mm^2, with excellent stone free rates up to 95% in one procedure. However, PNL is associated with increased complication rates when compared to SWL or f-URS (11). Renal parenchymal injury is ineluctable in PNL procedure and adjacent organ injuries mostly occur while performing access. In cases where multiple kidney stones are located in more than one location, one access may not be enough.

Figure 2 - Comparison of post operative stone free status and complications between patients with and without lower calyceal stone, in multiple stone group.



Previous studies had demostrated that multiple access was associated with a greater amount of blood loss, discomfort and renal function deterioration.

We achieved 92.7% and 86.4% stone free status in patients with solitary renal stone and multiple renal stones, respectively. Both Breda et al. and Huang et al. reported 100% success with f-URS in multiple renal stones under 20mm (12, 13). However, their study samples involved less number of patients when compared with our study and included 51 and 25 patients, respectively. Additionally, we performed only 3 (2.3%) second f-URS procedure in patients with multiple renal stones. In Huang's study, 9 patients (36%) required second f-URS procedure and 2 patients (8%) required third f-URS procedure. Similarly, Breda et al. performed 1.4 f-URS procedure while getting a 100% success rate. Additionally, focusing the stone during stone fragmentation is more difficult in hydronephrotic cases, due to increased mobility of the stone. We have encountered more hydronephrotic cases in group 2 and this might be another reason for lower stone free rates and longer operation time in this group.

Treatment of lower pole stones is challenging for urologists because of anatomic variabilities and technical conditions. Nonetheless, we did not shown any significant difference on success in patients with multiple stones, whether patients have lower pole stone(s) or not (p=0.856). Similar to our results, Jacquemet et al. compared 139 and 232 f--URS procedures for stones located in a single renal location other than the lower pole and at least one stone located in the lower pole, respectively. They did not found any impact of lower pole localization on f-URS success (14). Although preoperative characteristics were well matched between our patients with multiple stones, we compared only 92 patients and 19 patients, with and without lower pole stones, retrospectively. We believe studies with high patient volume will clarify this issue.

Table 4 - Operative and post-operative characteristics of patients with multiple renal stones according to absence/presence of lower pole stone.

	Lower calyceal stone present	No lower calyceal stone	P value
Number	92	19	
Type of f-URS			0.810
Flex-X2 (Fiberoptic)	72	15	
Dur-D (Digital)	20	4	
Mean operation time(minutes)	47.1±22.1	51.5±23.2	0.431
Mean fluoroscopy time(minutes)	2.6±1.4	2.3±1.8	0.436
Mean hospitalisation time(hours)	21.1±13	29.3±28.5	0.052
Post operative complications			0.616
Severe pain (grade 1)	14(15.2)	2(10.6%)	
Need for antibiotic change due to fever (grade 2)	4(4.4%)	1(5.3%)	
Gross bleeding (grade 1)	1(1.1%)	1(5.3%)	
JJ Catheter migration (grade 3a)	1 (1.1%)	0	
JJ Catheter migration (grade 3b)	1 (1.1%)	1 (5.3%)	
Peroperative success			0.856
Stone free status	80(87.0)	16(84.2%)	
Residual stone	12(13.0)	3(15.8%)	
Need for additional procedures	2(2.2%)	1(5.3%)	0.153
Stone analysis			0.977
Calcium oxalate monohydrate	31	6	
Calcium oxalate dihydrate	13	2	
Uric acid	2	0	
Cystine	6	1	
Struvite	2	0	
Mixt	11	2	

JJ Catheter = Double-J catheter

The mean operation time was longer in patients with multiple renal stones (47.8 min vs. 44.6 min) but the difference was not statistically significant (p=0.229). We believe that determining the location of the stones in different localizations and focusing with the laser is a time consuming process. Our operation time was found shorter compared to similar studies which evaluate operation time in multiple renal stones. The mean operation time was 65.1 min in Breda's study but they calculated the operation time from the time of cystoscope insertion to the stent placement, different from our study. Additionally, their study included patients with 20mm stone size (12). Huang et al. calculated the operation time similar to our study but they informed the mean operation time per patient (81.2 min) including second and third procedures, if necessary (13).

We found that the mean fluoroscopy screening time was significantly longer in patients with multiple renal stones (p=0.043). Previous reports discussed above did not mention about fluoroscopy screening time. However, we are aware that our fluoroscopy screening time

was longer when compared to other f-URS studies in the literature. We believe that our tendency to frequently determine the location of the stone with retrograde pyelography and aid fluoroscopy screning to find the stone(s) resulted in longer fluoroscopy screening time.

Complication rates were 15.3% and 23.4% in patients with solitary renal stone and multiple renal stones, respectively but difference was not statistically significant. We did not face any Clavien 4 and Clavien 5 complications. Severe pain was the most common post operative complication in both groups. Urinary tract infection was seen only in the multiple renal stones group. We deemed that more manipulation in multiple renal stones was related with severe pain and infectious complications. Double-J stent migration was identified in five patients with a kidney – ureter – bladder radiogram postoperatively. The double-J stent was reinserted under local anesthesia in two patients (Clavien 3a) and under general anesthesia in three patients (Clavien 3b), respectively.

Although with sufficient number of patients, our study has some limitations. First of all, we are aware of the retrospective nature of our study. Secondly, we did not evaluate the need of analgesic requirements postoperatively and cost of our procedures. Also, comparison of the presence of lower pole stones were made between unevenly numbered groups. Additionally, our stone analysis datas are incomplete, which is another limitation of our study. Our Ministry of Health does not provide a free 'Stone analysis' for every patient, thereby, only 132 of our patients had stone analysis results. Finally, secondary procedures for residual stone fragments was not commonly applied to our patients, because most of our patients were symptom-free and did not want to undergo a secondary procedure.

CONCLUSIONS

Our study has showed that f-URS achieved better stone free status in solitary renal stone than multiple renal stones under 300mm^2. However, stone free status and complication rates of f-URS were acceptable in patients with multiple stones. To our knowledge, this is the first study which compares the effect of multiple stones or single stone on the outcomes of f-URS. However, our findings must be supported by further prospective, randomized studies with large patient volume.

ABBREVIATIONS

SWL = Shock Wave Lithotripsy
PNL = Percutaneous Nephrolithotomy
F-URS = Flexible ureterorenoscopy
IVU = Intravenous urography
CT = Computed tomography
BMI = Body mass index
Min = Minutes

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Outcome analysis of holmium laser and pneumatic lithotripsy in the endoscopic management of lower ureteric calculus in pediatric patients: a prospective study

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ABSTRACT

Objective: To analyse outcomes of holmium laser and pneumatic lithotripsy in treatment of lower ureteric calculus in pediatric patients.
Materials and methods: Prospective study conducted between August 2013 and July 2015. Inclusion criteria were lower ureteric calculus with stone size ≤1.5cms. Exclusion criteria were other than lower ureteric calculus, stone size ≥1.5cms, congenital renal anomalies, previous ureteral stone surgery. Patients were divided into two groups. Group A underwent pneumatic and group B underwent laser lithotripsy procedure. Patient's baseline demographic and peri-operative data were recorded and analysed. Post operatively X-ray/ultrasound KUB (Kidney, ureter and bladder) was performed to assess stone free status.
Results: A total of 76 patients who met the inclusion criteria to ureteroscopic intracorporeal lithotripsy were included. Group A and B included 38 patients in each. Mean age was 12.5±2.49 in Group A and 11.97±2.74 years in Group B respectively (p=0.38). Overall success rate was 94.73% in Group A and 100% in Group B, respectively (p=0.87).
Conclusion: Holmium Laser lithotripsy is as efficacious as pneumatic lithotripsy and can be used safely for the endoscopic management of lower ureteric calculus in pediatric patients. However, holmium laser requires more expertise and it is a costly alternative.

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Lithotripsy, Laser; Ureteroscopy; Pediatrics

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INTRODUCTION

The incidence of stone disease in the pediatric age group is on the rise particularly in developing nations like India. Management of ureteral stone in pediatric age group is often challenging. Open ureterolithotomy was the preferred treatment for ureteral stone before 1980's (1). With the improvement in surgical skills and technological advancement of the endoscopic instruments, the management of ureteral stones in children is becoming more similar to that in adults, and it has changed from more invasive open surgeries to less or minimal invasive endoscopic lithotripsy. Pneumatic and laser lithotriptors are most preferred and frequently used in intracorporeal lithotripsy during endoscopic management of ureteral stone (2). Holmium Laser lithotripsy now gained popularity and is established as standard modality (3). With the introduction of holmium YAG laser in the urological armamentarium indications for ureteroscopic stone managements have extended and now it is possible for the urologist to also manage larger stone sizes (4).

Material and methods: This prospective study was conducted after obtaining ethical review board committee approval and an informed written consent was signed from all the included patients/parents/guardians in the department of Urology of a tertiary care teaching institute situated in north India from Aug 2013 to July 2015. A total of 76 patients of 6-17 years of age met the inclusion criteria of having lower ureteric calculus (≤1.5cms) as evident by symptoms and radiological investigation (X-ray KUB/Ultrasound KUB/ Computed tomography of KUB (Kidney, ureter, and bladder region). Exclusion criteria were other than lower ureteric calculus, stone size ≥1.5cms, congenital renal anomalies, history of ureteral stone operation, active urinary tract infection, spinal deformities, bleeding diathesis.

Prior to intervention patients underwent complete physical examination, urine routine with culture and sensitivity, and blood investigation. The site and size of ureteral calculus was noted. Appropriate antibiotic was administered pre and post intervention. Patients were allocated into either group A or group B in 1:1 ratio. Group A patients underwent pneumatic lithotripsy and group B underwent holmium laser lithotripsy. Patients were followed with X-ray KUB/USG KUB region and note of complaint if any. Operating time was calculated from insertion of pediatric cystoscope into meatus to the removal of ureteroscope out of meatus.

Technique

Both the ureteroscopic procedures were done under general anaesthesia in lithotomy position. A rigid cystoscopy was performed to locate ureteric orifice and advancement of hydrophilic guidewire under fluoroscopic guidance into the renal pelvis or beyond the level of calculus. Ureteral orifice was dilated with a balloon catheter (whenever indicated). A 6 to 7.5F semirigid ureteroscope (Karl Storz) was used for ureteroscopic lithotripsy. Post operatively fluoroscopy was performed for reassessing any residual and position of double J stents. Ureteroscopy performed, ureteroscope placed distal to stone, the holmium laser fibre (365µm) pulse frequency: 8-10Hz, and power supply: 9.6-16W was used in group B and Swiss lithoclast 2 device (Wolf) with 3F pneumatic probe was used in group A for lithotripsy. Stone was fragmented and retrieved and very tiny fragmentes were left for spontaneous passage. Double J stent was inserted in all patients. Foley catheter was placed post operatively. On postoperative day 2, stone-free state was checked with KUB films. Impacted calculus was defined as stone which did not change its position for at least 3 months.

Statistical analysis

The results are presented in mean±standard deviation (SD) and percentages. The unpaired t--test was used to compare two independent means. The p-value <0.05 was considered statistically significant. All the analysis was carried out using SPSS 16.0 versions (Chicago, Inc., USA).

RESULTS

Baseline demographics were comparable in both the groups (Table-1). A total of 76 (male: 66, female: 10) patients who met the inclusion criteria for endoscopic intracorporeal lithotripsy were included in the study. Group A and B both consisted of 38 patients each. Mean age was 12.5±2.49 years in Group A and 11.97±2.74 years in Group B respectively (p=0.38). In laser lithotripsy group 28 patients had right and 10 had left ueretric calculus while in pneumatic lithotripsy group 26 patients had right and 12 had left ureteric calculus. Stone surface areas were 8±3.09mm^2 in group A and 8.2±3mm^2 in the in group B respectively (p=0.77). Total operative times in group A was 37.13±5.94 min and in group B was 40.15±5.5 min respectively (p=0.023). Mean per urethral catheter duration in both groups was 12 hrs following endoscopic lithotripsies. Lengths of the hospital stay in group A was 2.45±0.49 and 2.27±0.43 days in group B (p=0.09). Two patients (5.62%) in group A and 3 patients (7.89%) in group B had fever (≥38.5^{o}C) which was managed conservatively. None of our patients experienced any major complication related to the procedure. Stone migration was observed in 2 (5.62%) patients in group A (Table-2). Antibiotic was given according to urine culture sensitivity for one day before and after procedure.

Table 1 - Baseline characteristics of patients in both groups.

Parameters	Group A (Pneumatic)	Group B (Laser)	p value
No. of patients	38	38	1
Mean Age±SD	12.5±2.49	11.97±2.74	0.38
Male/Female ratio	34/4	32/6	
Laterality (R/L)	26/12	28/10	
Stone burden (in mm^2)	8±3.09	8.2±3	0.77
Prior intervention	Nil	Nil	NA
Impacted Calculus	2(5.2%)	3(7.89%)	1

Table 2 - Perioperative clinical data of patients in both groups.

Perioperative variables	Group A (Pneumatic)	Group B (Laser)	p value
Total operative time in (mins)	37.13±5.9	40.15±5.5	0.023
Foley catheter indwelling time in hours	12	12	1
Length of hospital stay(in days)	2.45±0.49	2.27±0.43	0.09
Double J stent	38	38	1
Complication			
Stone migration	2(5.2%)	0	0.49
Fever(≥38.5ºC)	2(5.2%)	3(7.89%)	1
Ureteric injury	0	0	
ESWL (auxillary Procedure)	2(5.2%)	0	0.49
Overall success rate (n%)	94.73%	100%	0.87

DISCUSSION

Lower ureteric calculus is not uncommon in pediatric age group. Different treatment modalities are available for the management of lower ureteric calculus for pediatric patients including ESWL (extracorporeal shock wave lithotripsy), ureteroscopy, percutaneous antegrade ureteroscopy, laparoscopic and open surgery (5). With the improvement in surgical skills and technical advancement in the working instruments (smaller calibre semi-rigid and flexible ureteroscopes), the management of lower ureteric calculus has changed from open surgery to minimal invasive endoscopic lithotripsies (6). In the current era, ureteroscopy has become the preferred modality of managing lower ureteric calculus with success rate approaching to 100% in both adults as well as in pediatric patients.

Young in 1912 was the first to perform ureteroscopy, inserted a cystoscope in a child with posterior urethral valve (7). Goodman in 1977 was the first to performed rigid ureteroscopy (8).

Different lithotriptors can be used for intracorporeal lithotripsy including electrohydraulic (EHL), ballistic (pneumatic), ultrasonic (US), laser (Ho: YAG). In the last few years lasers have been increasingly replacing others for intracorporeal lithotripsy (9, 10).

European Association of Urology (EAU) recommends Holmium YAG laser as gold standard procedure for intracorporeal lithotripsy (5). The reason behind is, its advantageous property

of breaking all type of stone irrespective of their composition as compared to other lithotriptors and because of weaker shock waves there is lower risk of stone migration (11).

Pneumatic lithotripsy was first introduced into practice in 1992 in Switzerland (12). Advantage of pneumatic lithotripter when compared to other lithotriptors is its lower risk of perforating ureter and no thermal damage (13). Only concern with pneumatic lithotripter is stone migration, that ranges between 1.6% and 17.3% particularly with upper ureteral calculus (14, 15).

In the present study stone-free rate for lower ureteric calculus with holmium laser was 100% and 94.73% with pneumatic lithotripsy respectively (p=0.87). This study confirms previous reports in literature about efficacy of ureteroscopic Ho: YAG laser lithotripsy in treating distal ureteric stones (16, 17). Total operative time in this study was 40.15±5.55 min in laser lithotripsy while 37.13±5.94 min in pneumatic lithotripsy (p=0.023). In this study we observe 100% success rate with laser lithotripter and 94.73% with pneumatic lithotripsy. Similarly, Salvado et al. (18) also reported 96% success rate of laser lithotripsy in the management of distal ureteral stone. Manohar et al. (19) reported 84% success rate with laser lithotripsy. Our overall success rate for lower ureteric calculus in pediatric age group approached 97% with the ureteroscopic procedure which was in accordance with the literature.

In our study we observed stone migration into the collecting system of two patients (5.2%) in group A patients (impacted calculus), which later was managed with ESWL (after 3 days), while none of our patients in group B experienced similar complication. Razzaghi et al. (2) reported higher incidence of stone migration into renal collecting system with pneumatic lithotripter (17.9%) particularly with upper ureteric calculus and no such complication in the laser group. Salvado et al. (18) reported statistically insignificant difference of stone migration between the two modalities of lithotripsy. Similarly, Manohar et al. (19) did not observed any statistically significant difference of stone migration rates between pneumatic and laser lithotripsy groups. This is because of the improvement in surgical skills and technological advancement.

In this study, we retrogradely inserted Double J stent in all patients. In our belief ureteral stenting with double J stent prevents postoperative sepsis, and ureteral mucosal edema, although there was no clear precise indication for ureteral stenting such as ureteral injury or perforation. However, there are several prospective randomized controlled trails comparing stented versus non stented ureteroscopic lithotripsy and they reported similar outcomes (20). In the present study, length of hospital stay was comparable and we did not found any statistically significant difference between the two groups (p=0.09). This might be because none of our patients in the study had suffered any major complication related to procedure. Some studies in the literature reported complication rate of ureteroscopy between 9-25%. However, incidence of major complication is less than 0.1% n (5). Stone analysis in our study showed ammonium acid urate and uric acid stones the predominant variety. The major advantage with the holmium laser lithotripsy when compared with pneumatic lithotripter is that laser lithotripter will fragment any stone irrespective of composition.

CONCLUSIONS

Both holmium laser and pneumatic lithotripsy are equally efficacious and can be used safely for the endoscopic management of lower ureteric calculus in pediatric patients. However, holmium laser requires more expertise and it is a costly alternative and comparatively more advantageous in impacted calculus.

CONFLICT OF INTEREST

None declared.

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Non-infected penile prosthesis cultures during revision surgery; comparison between antibiotic coated and non - coated devices

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ABSTRACT

Introduction: Aim of this study is to investigate bacterial growth on non-infected devices and compare antibiotic-coated and non-coated implants.
Materials and methods: The charts of 71 patients who underwent revision surgeries for penile prosthesis between 1995 and 2013 were reviewed. Of those, 31 devices were antibiotic-coated prostheses, while 40 of the implants were non-coated. Swab cultures were routinely obtained from corporal, pump or reservoir site during the operation. If a bacterial biofilm was determined on the prosthesis, it was also cultured.
Results: A total of 5 different organisms were cultured from 18 patients. Of them, 4 devices were antibiotic-coated and the other 14 were non-coated devices. Staphylococcus epidermidis was the most common organism, while Staphylococcus hominis, beta hemolitic streptococcus, Escherichia coli and Proteus mirabilis were also cultured. All patients who had positive cultures were treated with appropriate antibiotics for four weeks postoperatively. Median follow-up time was 41 months, ranging between 8 and 82 months. One prosthesis (non-coated) became clinically infected in the follow-up period with a totally different organism. Culture positivity rates of antibiotic-coated and non-coated devices were 13% and 35% respectively and the result was significant (p=0.00254).
Conclusions: Positive bacterial cultures are present on non-infected penile prostheses at revision surgeries in some of the patients. Antibiotic coated prostheses have much less positive cultures than non-coated devices.

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INTRODUCTION

Penile implants have been used for more than 40 years and are the standard of care for erectile dysfunction in patients who do not respond to medical treatment. The morbidity rate associated with penile implants is relatively low, and patient satisfaction is high owing to improvements in techniques, materials and design. Mechanical failure, which is the primary cause of reoperations following penile prosthetic surgery, has an incidence ranging from 0-56% in large series (1-4).

The most common cause of mechanical failure is fluid leakage from the device (5). Other reasons of revision include corporal deformity, aneurismal dilatation of the cylinders, lateral extrusion and the desire of the patient for upsizing (5). Infection represents one of the most serious complications of penile prosthesis implantation surgeries. The prevalence of PPIs in modern series is estimated to be between 1% and 3% for first (virgin) implantation and between 10% and 18% for repeat implantations (6, 7). Despite careful work and the use of copious antibiotic irrigation of the implant space and systemic prophylactic antibiotics, the incidence of infection ranges between 1% and 6.5% (1, 8). These rates may further decline by 50% with the use of drug-coated prostheses for both first--time and repeat implantations (9, 10). Although infection rates are low, morbidity due to infection is serious. Additionally, infection may result in corporal fibrosis and penile shortening. These complications are responsible for patient dissatisfaction and can render re-implantation difficult. An immediate salvage procedure with substantial success is used to prevent corporal fibrosis and penile shortening (11, 12).

Treatment of PPIs is difficult and costly, and the prevention of infections is accordingly of utmost importance. In the last 10 years, there have been some technical and device-related modifications that have been adopted to reduce the risk of infection associated with penile prosthesis surgery (13). After 2001, manufacturers began to coat penile implants with an antibiotic impregnated material in an attempt to protect the devices from revision surgery because of infection. However, the etiology of late prosthesis infection is still controversial. The effect of hematogenous seeding has been discussed by many authors but not proven yet. It has been shown that, the majority of clinically non-infected penile prostheses possess organisms growing in the implant space that were cultured during the revision surgery (14, 15). The bacteria are inoculated into the implant space during the implantation surgery because of local hematoma, edema, and necrosis. These bacteria secrete extracellular polysaccharide matrix called biofilm which enhances bacterial growth by acting as physical barrier to protect the bacteria from antibiotics and host defense mechanisms (15, 16). These bacteria remain dormant in the implant space and do not cause clinical infection for many years until they become planktonic (i.e., free-floating). At that time, the symptoms of an active infection are manifested. The effect of microorganisms that were cultured in revision surgeries has not yet been investigated.

In this study, we aimed to investigate bacterial growth on non-infected penile prostheses. We also compared antibiotic-coated and non-coated implants during the revision surgery.

MATERIALS AND METHODS

This study was a retrospective evaluation of prospectively followed patients who underwent penile prosthesis revision surgery due to non-infected causes. We prospectively obtained cultures in a standard manner from patients who underwent either revision or explantation of clinically non--infected penile prostheses. We focused on a total of 71 consecutive patients who underwent revisions for clinically non-infected reasons between 1995 and 2013. The patients underwent revision surgery for mechanical failure in 57 cases (80.2%), cylinder aneurysms in 3 cases (4.2%), impending erosion of the device in 4 cases (5.6%), patient dissatisfaction in 4 cases (5.6%), and undersizing in 3 cases (4.2%). There was no evidence of clinical infection in any patients prior to the revisions, and all of the patients had negative urine cultures. Thirty-one of the devices were coated with antibiotic, while 40 were non-coated. Swab cultures were routinely obtained from the corporal, pump or reservoir site during the operation. The cultures were obtained from all of the accessible components after removal using swabs of the surface of the device and peri-prosthetic space. If a biofilm was detected on any part of the prosthesis, an additional swab culture was obtained from that area. The collected samples were enclosed in air--tight plastic tubing and then transported to the microbiology test laboratory. The swabs were inoculated on blood sheep agar and EMB agar plates and incubated for 48 hours. The agar plates were examined after 24 and 48 hours. Bacteria

exhibiting growth were identified using standard techniques based on morphological, cultural and biochemical characteristics. Antimicrobial sensitivities were determined using the standard disc diffusion technique. Bacterial colony counts of the identified organisms were quantitated by our microbiology laboratory and reported.

All of the surgical procedures were performed by a single surgeon (MMC) according to standard surgical protocols (i.e., a penoscrotal incision). There were no complications during any of the surgeries. On the day of the revision surgery, all of the patients underwent a 10-minute skin preparation procedure with a povidone-iodine scrub. Furthermore, all of the patients received perioperative intravenous antibiotics (a combination of amikacin 500mg and teicoplanin 400mg). During the procedure, antibiotic irrigation was routinely performed on the surgical sites. A spray solution containing antibiotics was only used on the non-coated devices. All of the patients continued to receive intravenous antibiotics postoperatively until discharge. Fluoroquinolones were also prescribed for 7 days after discharge. All of the patients who had positive cultures were treated with appropriate antibiotics for four weeks postoperatively. After the revision surgery, urine and blood cultures were obtained from the symptomatic patients to evaluate the incidence of postoperative infections.

Different types of three-piece hydraulic prostheses were evaluated in this study. Either AMS (American Medical Systems, Minnetonka, Minnesota, USA) or Coloplast (Mentor Corporation, Santa Barbara, California, USA) penile prostheses were used in all of the patients. The prostheses not coated with antibiotics included AMS-CX, AMS-Ultrex and Mentor Alpha devices; the antibiotic-coated prostheses included AMS--CX and AMS-LGX-devices. The non-coated implants were old devices; they were used prior to 2000 and did not absorb antibiotics.

All of the data were collected from the hospital record system, and the study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Statistical analysis

All of the collected data were entered and analyzed using the SPSS 17.0 statistical program (SPSS Inc., Chicago, IL, USA). We used an independent sample t-test and Fisher's exact tests to compare the groups. Statistical significance was set at a p value of <0.05.

RESULTS

A comparison between the antibiotic-coated and non-coated groups is listed in Table-1. The mean ages of the patients in both groups were similar, as shown in Table-1. There were 9 and 11 patients with diabetes mellitus in the antibiotic--coated and non-coated groups, respectively; this difference was not significant (p>0.05). A total of 5 different organisms were cultured from 18 patients. Of these 18 devices, 4 were antibiotic coated and the other 14 were non-coated. Staphylococcus epidermidis was the most common organism; Staphylococcus hominis, beta hemolitic streptococcus, Escherichia coli and Proteus mirabilis were also cultured. Two different organisms were cultured simultaneously in two different patients in the

Table 1 - Comparison of characteristics of both groups.

	Antibiotic coated (n=31)	Antibiotic non-coated (n=40)	p
Mean age (years)	48.5	51.2	>0.05
Positive culture n (%)	4 (13)	14 (35)	0.002
Median follow-up (months)	29 (8 to 38)	53 (14 to 82)	<0.05
Mean revision time after first implant (years)	7.1 (2.4 to 8)	9.4 (0.8 to 17)	<0.05

antibiotic non-coated group and in one patient in the antibiotic coated group. A biofilm was detected in two patients, and the parts of the devices were also cultured. Staphylococcus epidermidis was cultured from both biofilms. The numbers of cultured organisms from both groups are listed in Table-2. The mean follow-up time was 41 months, with a range of 8-82 months. One prosthesis (non-coated) became clinically infected 17 months after the first revision surgery with a completely different organism (E. coli S. epidermidis). We cultured E. Coli from the non-infected prosthesis in the revision surgery. Later, the same prosthesis became clinically infected with S. epidermidis. The positive cultures rates of the antibiotic-coated and non-coated devices were 13% and 35%, respectively, and the difference was statistically significant (p=0.002). We found that antibiotic-coated prostheses had a culture positivity rate that was 62.9% lower than that of the non-coated group.

Within the antibiotic non-coated group, 20 patients had AMS-CX devices, 8 patients had AMS-Ultrex devices, and 12 patients had Mentor Alpha devices; in the antibiotic-coated group, 26 patients had AMS-CX devices and 5 patients had AMS-LGX devices.

DISCUSSION

While design modifications have decreased the incidence of mechanical failure, prosthesis infection remains a significant complication of penile implants. The incidence of PPIs associated with primary implantation is estimated to be between 1% and 3% for first implantation; the incidence of infection is higher after reoperation for revision or re-implantation (6, 7). Because treatment of these infections typically requires removal of the infected penile implant, preventing infections is crucial. It has been estimated that the majority of PPIs occur within the first year of implantation; the highest rate was noted within the first 3-6 months (17). In contrast, the mean revision time after implantation was 7.1 years in the antibiotic-coated group and 9.4 years in the non-coated group in our study Table-1. We believe that these long periods were due to lack of infection for revision surgeries.

Despite reducing the risk of infection with preoperative skin preparations, perioperative prophylactic antibiotics, copious irrigation with antibiotics and minimizing device-skin contact, the bacteria remains dormant on implants and may result in late prosthesis infection at later times. If revision of the device is necessary, the sequestered bacteria may be released and result in increased risks of infection in the new device (18). This situation may also lead to increased infection rates in revised penile prostheses.

Clinically apparent infections are related to the virulent species of bacteria and the host defense mechanisms. Patients with diabetes mellitus

Table 2 - Organisms cultured from uninfected penile prostheses during the revision surgery.

	Antibiotic coated (n=31)		Antibiotic non-coated (n=40)	
	Cultured from one component	Cultured from more than one component	Cultured from one component	Cultured from more than one component
Staphylococcus Epidermidis	2	1	6	3
Escherichia Coli	1	-	2	1
Beta hemolytic streptococcus	1	-	-	-
Staphylococcus Hominis	-	-	2	-
Proteus Mirabilis	-	-	2	-
None	27		26	

are more susceptible to developing infections as a result of high glucose levels that encourage bacterial growth. However, the number of patients with diabetes mellitus was not different significantly between our two study groups.

It has been shown that antibiotic-coated penile prostheses are associated with a lower risk of infection than non-coated devices. A recent study reported that antibiotic impregnated devices have a 1.62% infection-related revision rate; non-impregnated penile prostheses have a 4.24% infection-related revision rate at a 7 year follow-up. This difference was statistically significant (19). The authors concluded that the use of antibiotic-impregnated devices can decrease revision due to infection. Similarly, Wilson et al. found that antibiotic-coated penile prostheses resulted in fewer infections in virgin, non-diabetic and virgin, diabetic patients than non-coated prostheses (20). Controversially, these authors also found that antibiotic-coated devices used in revision surgery did not reduce the infection rate if the antibiotic wash-out was not applied. Carson et al. (17) compared infection rates between penile prostheses impregnated with InhibiZone and prostheses without antibiotic. They found that prostheses with InhibiZone had significantly lower infection rates than non-coated prostheses at all of the time points that they evaluated. The decrease in infection rates between the groups was the largest during the first 60 days of implantation (82.4%). After 180 days, the decrease fell to 57.8%, but it maintained a constant level thereafter. Carson et al. concluded that antibiotic-coated group exhibited a 56.5% decrease in infection rate compared with the non-coated group after 1 year of surgery. Although Carson et al. studied a different population than our cohort, we similarly found that antibiotic-coated prostheses had a culture positivity rate that was 62.9% lower than that of the non-coated group after a long follow-up period.

Bacteria are also cultured from the penile prostheses that were explanted during a revision surgery owing to non-infected causes. Licht et al. obtained cultures from 65 clinically non-infected penile prostheses and 22 artificial urinary sphincters during revision. These authors found that 43% of clinically non-infected penile prostheses (28 out of 65) exhibited a positive culture during revision surgery (21). Staphylococcus epidermidis was the most common isolated organism and was found in 26 out of 65 penile prostheses (40%). Licht et al. also found that 3 penile prostheses became infected during the follow-up period. However, this study was moderately early and published at the time when non-coated devices were being used commonly. In a more recent multicentric study spanning three institutions, penile prostheses cultures were obtained from 77 clinically non-infected penile prostheses during the revision surgeries (15). Microorganisms were cultured from 54 out of the 77 devices (70%). The authors also found that 49 out of 54 patients (90%) had positive culture for Staphylococcus genus; there were 10 different species. They additionally evaluated the sensitivity of organisms to rifampin and tetracycline (minocycline) and concluded that all of the staphylococcal species were sensitive to these antibiotics. Licht et al. focused on only non-coated penile prostheses and did not make a comparison between antibiotic-coated and non-coated devices. In an experimental study, Rajpurkar et al. (22) evaluated the effect of coating the surface of polyurethane (Bioflex) with a hydrophilic material with and without antibiotics. These authors quantified bacterial colony counts both in vitro and in rats. They found that bacterial colonization was the highest in the uncoated Bioflex material, followed by the uncoated Bioflex with the antibiotic treatment, coated Bioflex and coated Bioflex with antibiotic treatment. They concluded that coated Bioflex with antibiotic treatment resulted in a 55% reduction in bacterial count compared with uncoated Bioflex. Moreover, they also found that coated Bioflex without antibiotic treatment correspondeds to a 41% reduction in bacterial colonization compared with uncoated Bioflex without antibiotic treatment. The findings of this experimental study support our results that antibiotic-coated materials experience less bacterial colonization than non-coated materials. This conclusion may lead to a decreased late infection rate in antibiotic-coated penile prostheses. A study by Abouassaly et al. recovered findings similar to ours (23). The authors performed 55 replacements of penile prostheses due to reasons

independent of infections; no salvage procedures were performed. Abouassaly et al. found only one case of clinical infection with a median follow--up duration of 32 months. They concluded that antibiotic-coated penile prostheses may decrease infection rates in patients undergoing replacement procedures owing to causes other than infection.

Skin flora are the most common source of PPIs; those organisms are introduced at the time of device implantation. Staphylococcus epidermidis is the most common organism cultured in infected prostheses, and it accounts for 35-80% of all positive cultures (8, 24). Parsons et al. also showed that Staphylococcus epidermidis was the most common organism cultured from infected prostheses and urinary sphincters (25). Similarly, Staphylococcus epidermidis was the most common isolated organism from revised penile implants that were revised owing to causes other than infection (15, 21). These organisms are of low virulence and are accessed during the implantation and survive in a biofilm secreted by the bacteria themselves. Our results confirmed that Staphylococcus epidermidis is the most common cultured organism in uninfected, revised penile prostheses. Staphylococcus aureus and Escherichia coli have also been shown to play a role in PPI (21, 26, 27). We additionally cultured Staphylococcus hominis, beta hemolytic streptococcus and Proteus mirabilis from the non-infected devices.

This study had a few limitations. First, although the patients were followed prospectively, the data were collected retrospectively from hospital records. Second, there have been no similar and comparable studies in the literature with a large volume of data pertaining to non-infected penile prosthesis revision surgery and comparing antibiotic-coated and non-coated devices. Despite these limitations, this study for the first time clearly showed that antibiotic-coated devices result in less bacteria colonization on the implant and peri-prosthetic space compared with non-coated devices, a situation that may decrease the incidence of PPIs.

CONCLUSIONS

Based on our results, positive bacterial cultures are present on non-infected penile prostheses during the revision surgeries of some patients. Our results also suggest that, antibiotic-coated penile prostheses have less bacteria seeding on prostheses in revision surgeries. Therefore, antibiotic coating may prevent late PPIs, particularly after revision surgeries. We also confirmed that, Staphylococcus epidermidis was the most common cultured organism from uninfected penile prostheses during revisions.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Clomiphene citrate treatment for late onset hypogonadism: rise and fall

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ABSTRACT

Objective: Previous series have demonstrated that Clomiphene Citrate (CC) is an effective treatment to increase Total Testosterone (TT) in Late Onset Hypogonadism (LOH) patients. However, what happens to TT levels after ending CC treatment is still debatable. The objective of this study is to evaluate TT levels 3 months after the discontinuation of CC in patients with LOH who were previously successfully treated with the same drug.
Materials and Methods: Twenty-seven patients with LOH that were successfully treated (achieved TT levels >11nmol/l) with CC 50mgs daily for 50 days were prospectively recruited in our Andrological outpatient clinic. CC was then stopped for 3 months and TT levels were measured at the end of this period.
Results: Mean TT level before discontinuation of CC was 22.7±8.1nmol/L (mean±SD). Three months after discontinuation, mean TT level significantly decreased in all patients, 10.2±3.9nmol/l ($p<0.01$). Twenty-one patients (78%) decreased TT levels under 11nmol/L. Six patients (22%) had TT levels that remained within the normal recommended range (≥11nmol/l). No statistical significant differences were observed between both groups.
Conclusion: In the short term LOH does not seem to be a reversible condition in most patients after CC treatment. More studies with longer follow-up are needed to evaluate the kinetics of TT in LOH.

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INTRODUCTION

The exact prevalence of Late Onset Hypogonadism (LOH) is a matter of debate (1-3); however, there is consensus that it constitutes an emerging problem (4). Testosterone Replacement Therapy (TRT) using different formulations i.e. intramuscular, transcutaneous and trans-mucosal--among others-is the most popular treatment strategy for LOH (5). Based in clinical experience and following recommendations coming from guidelines, in most patients the indication of TRT may be clear; however, in some cases it may be controversial or even contraindicated. Examples of these situations are patients who want to father a child in the near future, in which TRT is contraindicated (6), patients with LOH symptoms-i.e. decreased sexual interest, erectile dysfunction-and Total Testosterone (TT) levels that are under but very close to the normal recommended range (11nmoL/L), in

whom the clinician may doubt whether the symptoms are really related to TT levels (7) or may be related to other conditions-i.e. psychological issues; and finally, men that may have transient hypogonadism (8, 9), for example due to stressful conditions (10). In these cases, but also in typical LOH patients, Clomiphene Citrate (CC) has become an extremely interesting alternative (11). Clomiphene Citrate blocks the estrogen receptor in the hypothalamus and pituitary gland, increasing FSH and LH levels and secondarily increasing spermatogenesis and testosterone levels (11, 12). Even though, Clomiphene Citrate treatment is not approved for men in many countries, it has been used over-the-counter for decades, first to improve sperm count and in the last 15 years it has proved to be an effective and safe strategy to increase testosterone levels in patients with LOH (13, 14). Clomiphene Citrate has advantage of not affecting fertility and not blocking the Hypothalamus-Pituitary-Testis (HPT) axis. However, information about CC treatment for LOH is still scarce, especially regarding the kinetics of TT levels and the potential recovery of HPT axis after treatment discontinuation. Taking this information into account, the objective of this study is to evaluate TT levels 3 months after the discontinuation of CC in patients with LOH who were previously successfully treated with the same drug.

PATIENTS AND METHODS

Thirty patients (mean 50.1 years, range 32-70) with LOH were prospectively recruited in our Andrological outpatient clinic. Late Onset Hypogonadism was defined according to previous consensus definition (15):

-Symptoms: decreased sexual interest, decreased morning erections, erectile dysfunction.

-Total Testosterone <11nmol/l (in at least two different measurements) Regarding symptoms, 13/27 patients complained of decreased sexual desire, 11/27 with Erectile Dysfunction (ED), and 3/27 both symptoms. The median IIEF-5 score of all patients before treatment was 18 (range 11-24). In the subgroup that complained of exclusively ED or decreased sexual interest plus ED the median score was 15 (range 11-19).

To be eligible to be treated with CC, patients had normal FSH and LH, no thyroid function abnormalities neither hyperprolactinemia. After a 50-day treatment with 50mgs of CC daily, twenty-seven patients achieved normal TT levels (>11nmol/l). In this specific sub-group (n=27) CC was stopped for 3 months and TT levels were evaluated at the end of this period. Total testosterone was analyzed using electrochemiluminescence inmuno assay (Roche™). LH and FSH were measured using direct chemiluminimetric inmuno assay (Siemens™). The study was approved by the Research Ethical Committee of Pontificia Universidad Católica de Chile.

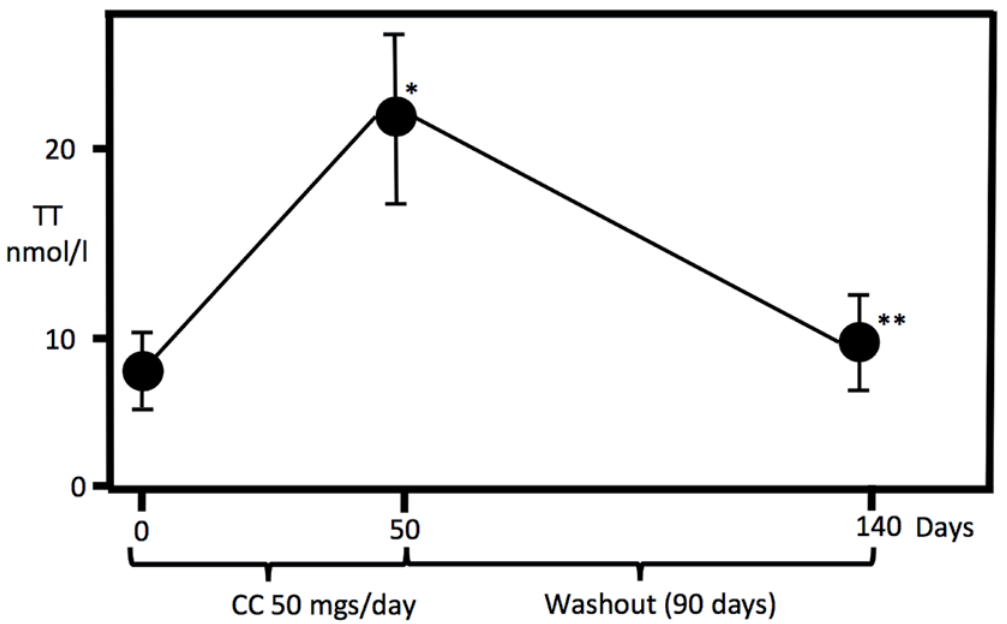
Statistical analysis

Data analysis was performed using GraphPad™ software. Differences in TT levels before and after discontinuation of CC were analyzed with paired t-test, considering statistical significance with a $p<0.05$. Results are shown as mean±SD.

RESULTS

Mean TT level at the time of diagnosis (n=30) was 8.5±1.8nmol/L (mean±SD), with normal range gonadotropins: FSH 5.1±4.9mIU/mL and LH 4.3±2.9mIU/mL. After a 50-day CC treatment, 27 patients achieved normal TT level. Mean TT level in this group was significantly higher than pre-treatment state, 22.7±8.1nmol/L, $p<0.01$ (Figure-1). Three months after discontinuation of treatment, mean TT level (n=27) was 10.2±3.9nmol/L. All patients (n=27) significantly decreased ($p<0.01$) TT after discontinuation of CC (Figure-1). Twenty-one (78%) patients decreased TT levels under 11nmol/L. Six patients (22%) had TT levels that remained within the normal recommended range (≥11nmol/L) three months after discontinuation of CC. This subgroup (n=6) was controlled six months after discontinuation of CC, in all cases TT decreased to the pre-treatment levels (<11nmol/L). No statistical significant differences were observed between the group of patients who maintained TT levels within the normal range (three months after discontinua-

Figure 1 - Total Testosterone (TT) levels at Day 0 (diagnosis), Day 50 (after Clomiphene Citrate (CC) treatment, 50mgs. daily), and Day 140 (90 days after ending CC treatment).



*p<0.01 between day 0 and day 50. **p<0.01 between day 50 and day 140.

tion) and those who decreased it (i.e. age, previous TT levels). Regarding symptoms, after increasing TT levels 38.5% (5/13) of patients who complained of decreased sexual desire improved the symptom, 27.3% (3/11) improved ED rising their IIEF-5 score (n=3) from a median of 18 (range 17-21) to 22 (21-24), and 2/3 (66.7%) improved both.

DISCUSSION

Testosterone replacement therapy has significantly increased in the last decade (16), however, everyday practice concerns are multiple (17). First: TRT is meant to be a lifelong treatment, so the decision of starting therapy is considerable, especially regarding long term safety issues-i.e. cardiovascular, oncological, etc., costs for the patient and finally the fact that if the treatment is stopped, testosterone levels will drop and may become even lower than the one that motivated TRT due to HPT axis blockade. Second: the two cardinal symptoms that usually motivate TRT are decreased sexual desire and ED. We know that the first is very sensitive to TT levels (18), however, extremely subjective. On the other hand, ED is associated with TT levels much lower than the lower range in which TRT is indicated (7, 18), so it may be incorrectly associated with TT levels that are low, but not low enough to explain the symptom. Third: TRT produces reversible infertility, which constitutes a problem in patients who want to father a child. Fourth: we do not know how many patients may present only a transient hypogonadism which could recover TT levels after a "stimulation" treatment, meaning that an undetermined number of LOH cases may not need a chronic treatment but a short-term therapy or an intermittent one (8, 9).

Taking all this information into account, therapy with CC makes sense and evidence supports it. The results of our series demonstrate that 90% of men with LOH increased TT under treatment which agrees with other reports showing that in selected patients, CC is efficacious in a high proportion of cases and has the advantages of not blocking the HPT axis, not affecting fertility, not producing polycythemia, and all with lower costs

than TRT (8, 19-21). Even an isomer of CC, Enclomiphene (EC), has been introduced recently, having the advantages of shorter half-life and theoretically more specificity to increase LH and FSH (22). EC has also demonstrated to increase testosterone levels in a high proportion of cases (23). So if CC or EC are such a good treatment, why not use it in all cases? And, if patients recover TT levels after a treatment with CC, is that recovery permanent once the therapy is cancelled?

Regarding the first question, it seems that one of the concerns would be the safety of the drug in the long term. Evidence suggests that long term CC treatment has no adverse effects and that efficacy is maintained, however, in the longer studies the follow-up does not exceed 46 months (14). In our study no adverse effects were reported; however, follow-up is too short to be conclusive.

The main objective of our study was to elucidate if LOH could be reversed by a 50-day CC treatment. Previous evidences were scarce, since most of the studies did not report the kinetics of TT after stopping CC treatment. We found three studies that reported TT level after ending treatment. Lim and cols. in 1976 reported in five hypogonadal uremic men an increase in TT levels after CC treatment that lasted for 12 months (24). Normal TT levels were reported 4 months after ending therapy. Guay and cols. in 2003 mentioned that in some patients with LOH, CC can be stopped and normal TT levels can be maintained (8). However, definitive data regarding this asseveration is lacking in the manuscript (8). Devoto and Aravena, reported that in a subgroup of patients with functional hypogonadotropic hypogonadism who respond to CC therapy, normal TT levels were maintained six months after ending treatment (9). On the other hand, Kaminetsky and cols, and Wiehle and cols. reported that in patients with secondary hypogonadism who responded to EC therapy, once the treatment was stopped TT levels decreased and returned to the pre-treatment values (23, 25). Our results concur with the last two authors since all patients decreased TT levels 3 months after discontinuation of CC treatment, 78% of them under the normal range. The six cases in which TT was in the normal range three months after CC discontinuation also dropped TT levels (to pre-treatment levels) six months after ending treatment. We think that our results reveal that LOH is a chronic irreversible condition in most cases. Since all cases dropped TT levels to pre-treatment levels we were not able to evaluate if certain patient characteristics (age, comorbidities, etc.) could predict a permanent response to CC treatment. The same occurred in the primary group (n=30) where 27 patients increased TT levels, making a comparison between responders and non-responders not statistically possible due to the small number of non-responder cases (n=3).

Considering our results and previous reports we think CC treatment would have three roles: First, it is an excellent alternative when patients are concerned about fertility, second, CC is an extraordinary alternative for a therapeutic individual trial in cases where we are not convinced that low testosterone is really the explanation to all its symptoms, especially when the TT level is very close to the normal ranges. Finally, CC represents a good alternative to TRT with the advantage of not blocking HPT axis, but taking into account our results and previous series (23, 25), it should be discussed with the patient that treatment will be permanent in most cases.

The main limitations of our study are: the short follow-up and the absence of the evaluation of estradiol and free testosterone. Regarding this last point, all patients had TT values under the normal range associated with symptoms, according to the guidelines in these cases TT would be enough for evaluation (5). Also no specific questionnaire was applied to the patients regarding LOH symptoms, however, these questionnaires are not recommended by the guidelines since their specificity is low and are not effective for case finding (5).

CONCLUSIONS

Late Onset Hypogonadism on men who successfully respond to CC therapy in the short term do not seem to reverse the condition after ending treatment. More studies with longer follow-up are needed to evaluate the kinetics of TT in these patients.

CONFLICT OF INTEREST

None declared.

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Medium-term results of Mini-arc for urinary stress incontinence in ambulatory patients under local anesthesia

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ABSTRACT

Objective: To evaluate the medium-term outcome and patient's satisfaction after Single-incision mini-sling (SIMS) procedure done under local anesthesia in ambulatory set up for patients with stress urinary incontinence (SUI).
Materials and Methods: This is a retrospective cohort study, including all patients submitted to SIMS procedure for SUI with MiniArc (AMS, U.S.A) without concomitant surgery between January 2011 and March 2013. Patients were followed up during 12 months after surgery and once a year subsequently. Telephone interviews were conducted to evaluate patient satisfaction. Outcome masseurs included: SUI cure rate, urinary urge incontinence (UUI) cure rate in patients with mixed urinary incontinence (MUI), intra and post-operative complications and patient satisfaction.
Results: Ninety-three patients were included with mean follow-up of 23 months. Fifty percent had MUI with predominant SUI. The cure rates of SUI (objective and subjective) were 89%. UUI was cured in 40% of patients. No major complications occur, neither voiding obstruction or groin pain. Telephone interviews conducted after 26 months on average revealed high satisfaction rate from the procedure (8.8 out of 10) and from the local anesthesia. Visual analog scale (VAS) rating was low during and after the procedure (2.38 and 2.69 respectively).
Conclusions: The SIMS procedure is safe and highly effective for SUI and it can be performed successfully under local anesthesia in an ambulatory setup.

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Keywords:
Urinary Incontinence, Stress; Anesthesia, Local; Patient Satisfaction

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INTRODUCTION

Stress urinary incontinence (SUI) affects the quality of life and wellbeing of approximately15% of the female population (1) and up to 35% of adult women worldwide (2). The treatment options for SUI include non-surgical options such as pelvic floor muscle training (PFMT) and surgical treatment. Surgery is generally more effective for severe SUI than PFMT is (3). The introduction of the mid-urethral sling (MUS) at the beginning of the 1990s by Petros and Ulstman (4) caused a complete shift from abdominal surgery, such as the Burch procedure, to the MUS procedures. Currently, MUS procedures are the most common and acceptable for SUI (5). Initially performed with retro-pubic approach, in the last ten years MUS procedures shifted toward the transobturator approach and toward single-incision mini-slings (SIMS), which help reduce complications of MUS such as hematomas, bladder perforation, groin pain, and obturator nerve capture (6).

Although the TVT-Secur (TVT-S, Ethicon, Summerville, USA), the first SIMS to be introduced, proved to be less successful than the retro-pubic and transobturator MUSs (7, 8), there are

many other SIMSs that provide excellent results, as good as MUS, with lower complication rates (9-14). All MUS procedures can be performed under general, regional, epidural, or local anesthesia, but the common practice for the retro-pubic and transobturator sling procedures is still to perform them under general or regional anesthesia, followed by one-night hospitalization with Foley catheter. There is economic advantage to an ambulatory setup (15), and there are first reports of SIMS performed as an outpatient procedure (2, 16).

Some studies have examined the efficacy of MUS on mixed urinary incontinence (MUI) by monitoring the improvement in urgency and urgency urine incontinence (UUI) (17, 18). However, in some of these studies, patients had a concomitant pelvic organ prolapse (POP) repair; therefore, the improvement of symptoms could have been related to the prolapse repair. Furthermore, most MUS procedures included in these studies were retro-pubic or transobturator, therefore data regarding the efficacy of SIMS on MUI are lacking.

The aim of the current study was to evaluate the medium–term outcome and patient satisfaction after the MiniArc (AMS, U.S.A) procedure performed mainly under local anesthesia in an ambulatory setup in patients with SUI or MUI, without comorbid POP.

PATIENTS AND METHODS

This is a retrospective cohort study that included all the patients at Ziv Medical Center who underwent the SIMS procedure with MiniArc (AMS, U.S.A) without concomitant surgery between January 2011 and March 2013. The study was approved by the local ethical committee. Data were collected from medical records, including demographic parameters: age, body mass index (BMI), parity, medical history and previous gynecological surgeries, and pre-and post-operative evaluation. Preoperative consultation included a structured questionnaire for symptoms of SUI, urgency, urgency incontinence, and nocturia. The clinical examination included the Cough Stress Test (CST) with a full bladder in supine position and pelvic organ prolapse-quantitative (POP-Q) examination to rule out significant pelvic organ prolapse. SUI was determined based on positive CST, with obvious urethral hyper-mobility. MUI was determined based on obvious symptoms of SUI and UUI, absence of neurological disease, negative urinary culture, and positive CST. Urodynamic tests were not performed routinely in the presence of a predominant SUI in non-complicated patients. Patients were evaluated 6 weeks, 6 months, and 12 months after surgery, and once a year subsequently. Follow-up evaluation included symptoms of SUI, urgency, UUI, and nocturia. Post-operative examination included CST with full bladder and vaginal examination for mesh erosion or pain. Operative failure was defined as ongoing symptoms of SUI or positive CST.

Additionally, a telephone interview was conducted to evaluate patient satisfaction with the procedure performed under local anesthesia and with the overall process. It was conducted by a medical student, as part of his graduate degree, and he was blinded to the results. The interview included 7 questions, which were answered subjectively by the women. Experienced pain was evaluated using the visual analog scale (VAS).

The MiniArc procedure was performed during day-care hospitalization and under local anesthesia. In rare cases, general or spinal anesthesia was used upon patient request or based on a narrow vaginal access. Intravenous prophylaxis, Cefazolin 2gr, was given preoperatively. There was no routine Foley catheterization during or after the procedure. Local anesthesia included the injection of 2 Ampules of Lidocaine 1% to the para-urethral space, from the vagina towards the obturator foramen on both sides. The vaginal wall was opened 1cm under the urethra and the para-urethral fossa was opened on both sides towards the obturator foramen with blunt scissors until the ramus of the pubic bone was felt. The sling was placed on a delivery needle, which was then inserted through the incision and into the obturator foramen, into the obturator internus muscle. This was repeated with the second sling tip on the contralateral side. Sling tension was controlled by the operator. Once the sling was deposited, the delivery device was removed and the incision was closed. Women were discharged after

spontaneous urination without urinary retention and residua.

Outcome measures included SUI cure rate in the entire group and in the MUI group, UUI cure rate in the MUI group, intra-and post-operative complications, and patient satisfaction.

RESULTS

Ninety-three women who underwent placement of the MiniArc without POP repair during the study period were included. One surgeon (NMB) operated all cases. Mean patient age was 53 years (range 33-75), mean BMI was 28 (range 16.8-41.9), and mean parity was 3.3 (range 0-8). Mean follow-up at the clinic was 23 months (range 12-48). Forty-seven out of 93 patients (50%) had MUI with predominant component of SUI. Seventy-eight patients (84%) were operated under local anesthesia. One patient (1%) was switched from local to general anesthesia during the procedure because of pain. No intra-operative complications were reported, and the majority of patients (92%) were discharged after three hours on average. Three patients stayed overnight because of a transient urinary retention, which was resolved after 12h with the use of a Foley catheter. The overall cure rate of SUI (objective and subjective) was 89% (83 patients) (Figure-1). Of the remaining ten patients, two cases were considered as failure and required a second procedure. In both cases urodynamic test was performed prior to the second procedure to exclude other pathology. The second procedure used was retro-pubic MUS and was successful in both cases. Eight patients reported partial relief. There were no major long-term complications (Table-1).

Twenty-three out of 47 patients (49%) with MUI, experienced complete disappearance of urgency and UUI after 6 months of follow--up, decreasing to 19 out of 47 patients (40%) after 12 months, without further deterioration in the long term (Figure-1).

The telephone interview was conducted 26 months on average after the procedure. Eighty out of 93 women (86%) answered the questionnaire, and their responses are summarized in Table-2. There was an overall high satisfaction with the procedure (8.8 out of 10), and VAS ranking was low during and after the procedure (2.38 and 2.69 respectively). Most patients (90%) were happy with the local anesthesia, and only 10% would have preferred to

Figure 1 - Stress urinary incontinence, urgency, and urgency urinary incontinence preoperatively, 6 months, and 1 year after MiniArc procedure. SUI – Stress Urinary Incontinence; UUI – Urgency Urinary Incontinence.

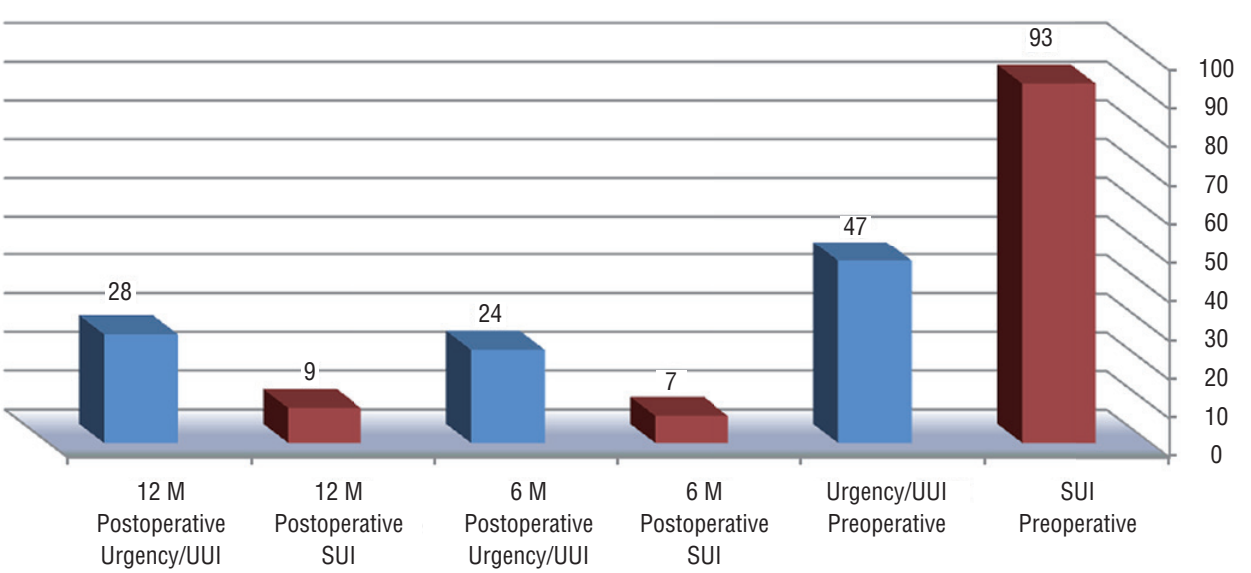

Table 1 - Long-term complications and treatment.

Complication N (%)	Detection	Treatment
Small mid-line erosion 2 (2%)	During first year	Removed under local anesthesia
Mesh penetrating the vagina (Unilateral) 2 (2%)	First follow-up	Mesh removed in OR[a]
Voiding dysfunction 1 (1%)	Immediate post-op[b]	Resolved spontaneously after 1 month
Groin pain – right due to hematoma 1 (1%)	Immediate post-op	Resolved spontaneously after 6 weeks
de novo UUI[c] 2 (2%)	First follow-up	Successfully treated with anti-cholinergic drugs

OR[a] = Operation room; **PO[b]** post-operative; **UUI[c]** = Urgency urinary incontinence

Table 2 - Results of the telephone survey.

	Average (range)	Range
1. What was the level of pain during surgery?	2.38 (0-10)	0-10 VAS
2. What was the level of pain after surgery?	2.69 (0-8)	0-10 VAS
3. How long did the pain last (in days)?	4.96 (0-90)	
4. How satisfied are you with the procedure?	8.82 (1-10)	0-10
5. Did surgery solve the problem?	Solved 68 (85%) Partial 10 (12.5%) Failed 2 (2.5%)	
6. Would you prefer a different kind of anesthesia for the operation you had?	No 72 (90%) Yes 8 (10%)	
7. Are you satisfied with the explanation about the procedure provided to you before the operation?	No 1 Yes 79	

undergo the procedure under general anesthesia because of pain.

DISCUSSION

Mid-urethral slings altered dramatically the treatment for SUI since they have been introduced by Ulmsten and Petros in 1995 (4). Complications of the retro-pubic MUS, such as vascular and bowel injuries, as well as bladder perforation and voiding dysfunction, led to the introduction of the transobturator MUS in order to decrease complication rates. Although the transobturator route reduced complications, it was associated with other complications such as vaginal penetration, de novo urgency, and persistent groin pain. Groin pain can be caused either by the passage of the mesh inside the obturator muscle or by contact with of the obturator nerve or even injury to it (6).

The aim of the SIMS procedure, first introduced in 2007 with the TVT-S, was to reduce MUS-related complications by obviating the need for the blind passage with trocars through the Retzius space or the transobturator foramen, and achieving the same success rate as other MUS

procedures. TVT-S did not stand up to expectations, and success rate was around 60%, as reported in many studies (19, 20). Other SIMSs appeared in the course of 2008 and thereafter, providing better results than the TVT-S did, and reducing complication rates (9-14). In 2011, TVT-S was still dominant in the market; therefore the meta-analyses that compared the transobturator and the retro-pubic MUS with SIMS included mainly studies involving TVT-S, and concluded that SIMSs are inferior to other MUSs (7). But recent meta-analyses that compare the results achieved with SIMS to those achieved with other MUS showed SIMSs to be highly promising, if studies with TVT-S are excluded from the sample (21). Therefore, we can conclude that not all SIMSs are the same, and that currently there are quite a few SIMS (MiniArc among them) that provide high success rate and few complications. However, more prospective randomize trials should be performed to compare between MUS and SIMS before final conclusion.

Performing the procedure under local anesthesia in an ambulatory setup has many advantages: significantly reducing the high cost of inpatient hospitalization and patient recovery (15), reducing anesthesia-related complications, and achieving high patient satisfaction with the procedure. In our study we found that patient satisfaction was very high (8.8 out of 10), and the majority of interviewers answered that they did not regret undergoing the procedure in this form. The process of administering local anesthesia involves certain difficulties, because the surgeon must rely on patient's cooperation. We assume that the lack of such cooperation was the reason for vaginal penetration in the first two cases. Careful examination at the end of the procedure can prevent this outcome. Although the procedure under local anesthesia can be technically somewhat more challenging, the present study demonstrated a high long-term success rate.

SUI is the most common form of urinary incontinence, occurring in pure or mixed forms in nearly 80% of women with incontinence (22). Patient history, symptoms, and physical examination (including positive CST) can identify most patients with a significant stress incontinence component. Urodynamic tests are controversial in cases of pure SUI, when urethral hypermobility is present. According to the studies by Nager and the Urinary Incontinence Treatment Network (23), a basic assessment for women with uncomplicated predominant SUI, who show stress incontinence on outpatient evaluation, is not inferior to a preoperative evaluation that also includes urodynamic testing. That routine urodynamic tests are unnecessary in relation to post-operative complications was also demonstrated by a recent meta-analysis, where the authors concluded that "In women undergoing primary surgery for SUI or stress-predominant MUI without voiding difficulties, urodynamics does not improve outcomes-as long as the women undergo careful office evaluation" (24). In the Ob/Gyn Department at Ziv Medical Center, urodynamic tests are not performed routinely in cases of predominant SUI without POP and before the primary operation. Although almost 50% of patients had MUI, all cases undergoing primary surgery had predominant SUI.

The telephone interview, conducted 26 months on average after the procedure, demonstrated a high satisfaction rate with the entire process and with the local anesthesia. Eighty-five percent reported complete cure, 12.5% partial cure, and only 2.5% reported that the procedure has failed. These numbers are somewhat different from the results in the clinic (89% complete cure), which may be explained by the nature of question 5 (Table-2), which asked whether the operation resolved the problem without addressing the SUI symptoms specifically, therefore women still suffering from UUI may have reported "partial relief."

The present study has some limitations because of its retrospective nature, therefore interpretation of the data may be biased. Since there are no validated questionnaires in Hebrew regarding satisfaction, we used a built questionnaire which is a drawback. Moreover, the questionnaire includes questions about the pain experienced during and after surgery, the answers to which may be less than accurate, because of the time elapsed after surgery.

The strength of this study lies in the fact that it reports on a one-center experience, with procedures performed by the same surgeon, therefore there were no differences in surgical technique and

protocol. All the patients in this group underwent surgery for SUI without concomitant prolaps repairs, therefore without any undesirable effect on functional or anatomical results. Finally, data collection from patient files was done by a medical student who was not involved in the surgeries. The telephone interview was conducted by an investigator who was blind to the data collection results, represented by a combination of questions about stress and urge incontinence.

CONCLUSIONS

We found that the SIMS procedure with the MiniArc system is safe and highly effective for SUI. The procedure can be performed in an ambulatory setup and under local anesthesia, with excellent results and patients' satisfaction.

CONFLICT OF INTEREST

None declared.

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Rate of spontaneous voiding recovery after acute urinary retention due to bed rest in the hospital setting in a non-urological population clinical study of the relationship between lower limbs and bladder function

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ABSTRACT

Objectives: To understand the clinical relationship between lower limbs functions and the recovery of spontaneous voiding after an acute urinary retention (AUR) in older patients admitted to hospitals for non-urological causes using clinical parameters.
Materials and Methods: 56 adult patients (32 men; mean age: 77.9 ± 8.3 and 24 women; mean age 82.1 ± 4.6) with AUR were prospectively followed with validated Physical Performance Mobility Exam (PPME) instrument to evaluate the relationship between the recovery of mobility capacity and spontaneous voiding. After a short period of permanent bladder drainage patients started CIC along evaluation by PPME during hospitalization and at 7, 15, 30 60, 90, and 180 days of discharge. Mann-Whitney U, chi-square test and ANOVA tests were used.
Results: All patients were hospitalized for at least 15 days (Median 26.3 ± 4.1 days). Progressive improvement on mobility scale measured by PPME was observed after leaving ICU and along the initial 7 days of hospitalization but with a deterioration if hospitalization extends beyond 15 days ($p<0.03$). Prolonged hospital stay impairs mobility in all domains ($p<0.05$) except step-up and transfer skills ($p<0.02$) although a recovery rate on spontaneous voiding persistented. Restoration of spontaneous voiding was accompanied by improvement on mobility scale ($p<0.02$). Recovery of spontaneous voiding was markedly observed after discharging the hospital. All patients recovered spontaneous voiding until 6 months of follow-up.
Conclusions: Recovery to spontaneous voiding after acute urinary retention in the hospital setting may be anticipated by evaluation of lower limbs function measured by validated instruments.

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INTRODUCTION

Diminished independence of hospitalized older people is associated with an increased risk of transfer to nursing homes, mortality and health-care costs after hospital discharge (1).

Patients resting or immobilized in hospital beds are a common clinical situation in different disease states. Frail older patients more commonly experience bed restriction during their recovery from the primary disease due to established generalized weakness or loss of consciousness (2).

In many circumstances, comorbidities are the decisive contributors to frailty and the inability to void, leading to secondary acute urinary retention (AUR) and permanent bladder drainage. Restoration of spontaneous voiding is a stressful event in the hospital setting because it can hardly be predicted, extending the period of undesired hospitalization even after general clinical improvement.

We hypothesized that diminished leg activity due to bed restriction secondarily predisposes patients to AUR resulting from the impaired neurogenic input from the neural sacral roots and poorly understood neurotrophic factors. Therefore, restoration of spontaneous voiding after a period of bed rest may be parallel to the functional recovery of the lower limbs.

MATERIAL AND METHODS

During an 11-year period (1999 to 2010), 63 consecutive patients were prospectively enrolled from a general internal medicine ward after a urological evaluation was requested by the admitting Intensive Care Unit (ICU) team due to a palpable suprapubic mass and/or pain, absence of urine output or paradoxical incontinence. Seven cases were unsuitable for completion of the entire study period (3 cases died during hospitalization; 3 cases decided to have permanent urethral catheterization and 1 case was permanently disabled), leaving 56 consecutive patients (32 men; mean age: 77.9±8.3 and 24 women; mean age 82.1±4.6) that were closely followed according to the established protocol after an urological evaluation was requested due to AUR in an adult general hospital.

Patients with chronic neurological conditions such as brain or spinal cord injuries, peripheral or post-operative neurological diseases, end-stage oncological disease, alcoholism, psychiatric disorders or drug abuse as well as acute or chronic use of cholinergic or anticholinergic agents were not accrued for the study.

Patients were also excluded if they could not follow simple commands and cooperate with the protocol, were delirious, had unstable fractures, had unstable cardio-respiratory status; had paraplegia or a major limb amputation, were demented or presented an impaired Folstein Mini-Mental State Examination (MMSE - score <24).

All patients or their responsible party reported they were able to walk across a small room without the assistance of another person prior to the hospital admission and were able to void normally with no previous urological evaluation or surgery to treat any dysfunctional voiding.

The inability to void was observed by the initial attending physician who requested a urological evaluation after hospital admission for various clinical reasons, none of them primarily related to urological problems (Table-1).

After careful urological evaluation, if the patient was unconscious or impaired to initiate a clean intermittent catheterization (CIC) regimen, they were spared from the study until they recovered and cooperated with the maneuvers described below to try to reestablish spontaneous voiding.

Patients first admitted to the ICU and who developed AUR received permanent urethral catheter until they could understand, cooperate and leave the bed. If the patient stayed in the ICU but was restricted to the bed, the protocol was postponed until they were discharged to the ward where the spontaneous voiding trial could be initiated, based on improvements in the general clinical condition as well as on consciousness and the ability to leave the bed.

If they were initially evaluated at the ward due to AUR and were not cognitively impaired or restricted to the bed, they had a permanent urethral catheter for 3 days after restoration of spontaneous voiding was attempted. If spontaneous voiding was restored post-void, residual and AUR were ascertained for 2 days before the patient was discharged. If the patient could not void after 3 days on a permanent urethral catheter, then the CIC regimen was initiated on the 4th day every 4-6 hours or on demand until the patient could void spontaneously, maintaining CIC for an additional 2 days after reestablishing spontaneous voiding to ascertain that post-void residue was consistently <100mL. If the patient was discharged from the hospital during this period, instructions were maintained for further urological follow-up. An auto-catheterization regimen was strongly stimulated, but a third-person caregiver was also instructed on the urethral catheterization in case of necessity or lack of autonomy.

Table 1 - Demographics of patients and main clinical reason for the admittance to the hospital before having urological evaluation and diagnosed as acute urinary retention after hospitalization.

Reason for Hospitalization	Men	Women
Age (±SD)	77.9 ± 8.3	82.1 ± 4.6
Protracted abdominal operation	7	9
Diabetes mellitus decompensation	6	4
Myocardial infarction	6	2
Pneumonia	4	3
Hip fracture	4	3
Diminished consciousness at home (mainly dehydration)	2	3
Acute Stroke	2	1

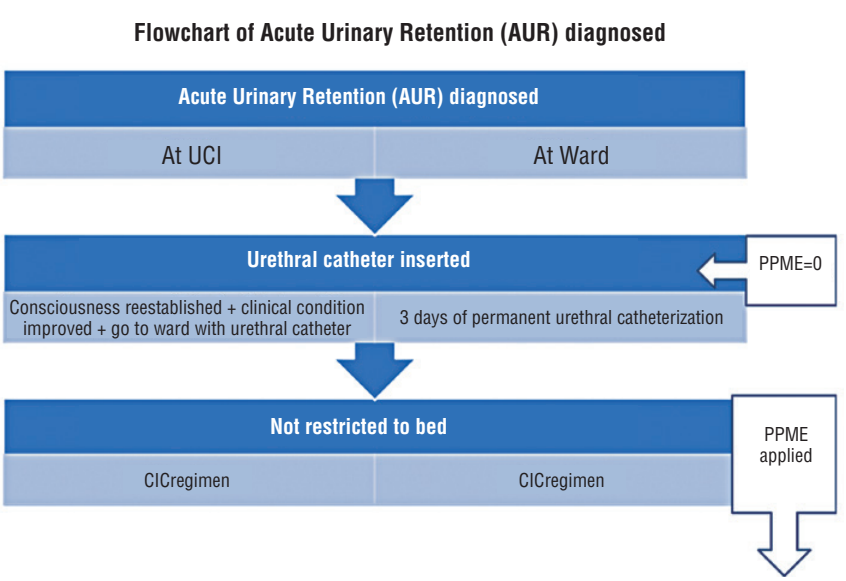
At the time of catheterization and inclusion in the study, the Physical Performance Mobility Exam (PPME) was scored as zero. Subsequent PPME evaluations were performed during periodical urological office or home visits at 7, 15, 30 60, 90, and 180 days after discharge (Figure-1).

PPME was used by assistant personnel as a tool to objectively characterize the mobility scale (3) on a weekly basis until hospital discharge and on programmed domiciliary or office visits as described and graphed. PPME was also applied in a retrospective manner by the familiar or third-party caregiver if the patient was admitted unconsciously.

The standard of care for the physical rehabilitation program included respiratory exercises and motor activities coached by a licensed physiotherapist twice a day during the hospitalization period (morning and evening).

Upon hospital discharge, patients were required to be able to stand and walk independently. No further coached physical therapy by a physiotherapist was carried out at home, although basic

Figure 1 - Period of hospitalization and discharge rate of 56 patients admitted for acute conditions.



exercises and walking at home at least 4 times a day was strongly reinforced.

Differences among the assessments of the physical domains throughout the study were performed using multivariate analysis of variance (ANOVA). Univariate analyses from the general linear model were also reported. Between groups of physical domains of PPME and in comparison to the rate of recovery of spontaneous voiding, factorial ANOVA for continuous measures, Mann-Whitney U and chi-square tests were used.

Medians were used to construct the presented graphics with standard deviation removed to facilitate graphical viewing. The IRB of the two involved hospitals approved the study.

RESULTS

A total of 48 cases were evaluated at the ward, whereas 8 were evaluated at ICU. Four patients were not unconscious, but they were cognitively impaired, impeding any prompt attempt to restore spontaneous voiding or start CIC. These cases were kept on permanent urethral Foley catheter until they could cope with the maneuvers (7, 7, 9 and 12 days, respectively).

Four patients presented overflow incontinence.

All 56 studied patients were hospitalized for at least 15 days with a decreasing number of cases, extending the hospitalization period beyond 30 days, as depicted in Figure-2. The median time of hospitalization was 26.3 days (SD±4.1 days).

Four patients promptly reestablished spontaneous voiding after the catheter was removed, but recurred on the AUR during their stay at the hospital. They were recorded as initiating the protocol from the point at which they started CIC.

Figure-3 shows that there were 3 points of inflexion regarding the evolution of mobility. The first inflexion concerns the significant improvement in the mobility scores at 7 days of hospitalization, possibly paralleling clinical improvement ($p<0.002$).

However, additional time in the hospital further impaired the mobility index when measured as the capacity to move on the bed, stand from a chair, equilibrate and walk ($p<0.03$). It is remarkable that those parameters worsened further until 30 days of hospitalization when the patient remained in the hospital ($p<0.02$).

Seven days after hospital discharge, a continuous trend of improvement in the mobility

Figure 2 - Flowchart of Acute Urinary Retention in 56 patients admitted to hospital due to other than urological condition.

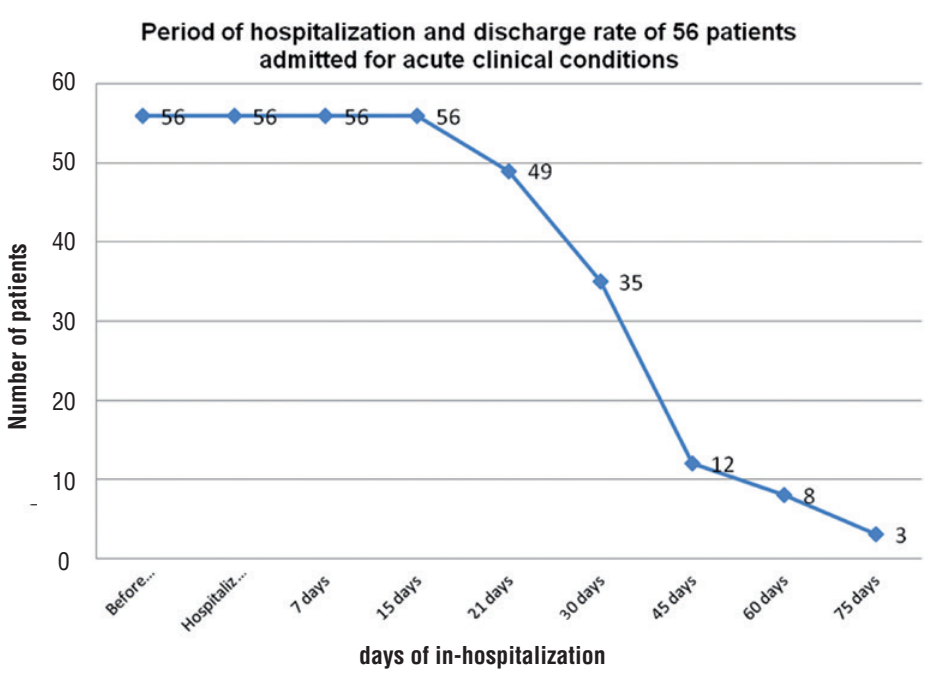
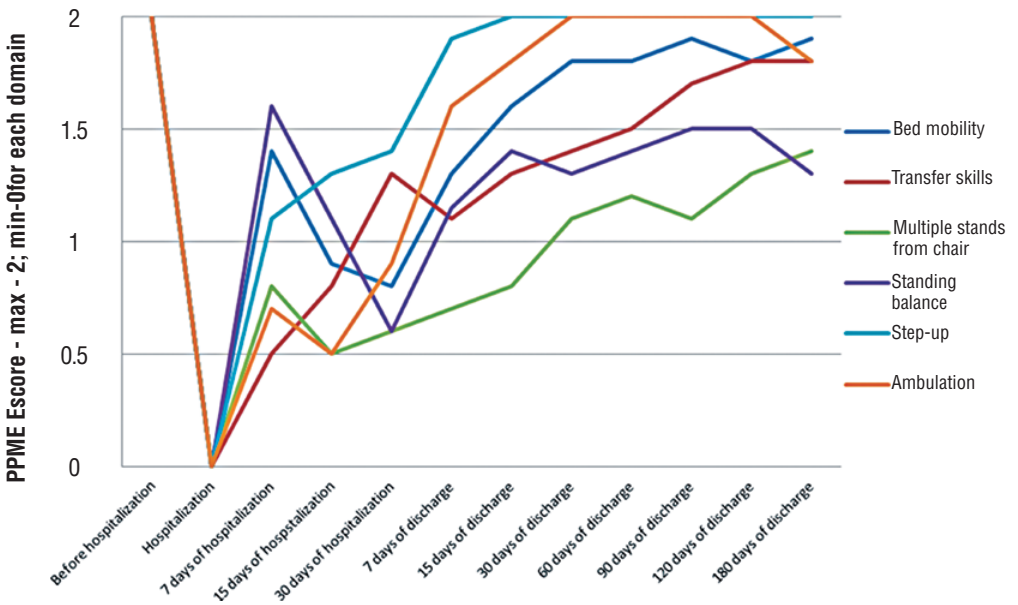


Figure 3 - Evolution of PPME by each domain along 180 days of study.



indexes was followed by a steady recovery in the capacity to void spontaneously ($p<0.03$).

Figure-3 also showed that some physical capacities improved faster than others with some improvement in a steady fashion, whereas others, such as bed mobility, standing balance and ambulation, obeyed the previously mentioned impairment if hospitalization extended beyond 7 days, further improving after hospital discharge ($p<0.05$).

Notably, after urinary retention was established and diagnosed, spontaneous voiding was recovered and paralleled the improvement of the PPME index, although an initial decrease in the average physical ability was measured in the initial 15 days of hospitalization, which did not impact the recovery of voiding (Figure-4).

It was also noted that 4 patients died during the 180-day follow-up period, although all patients were spontaneously voiding 90 days after hospital discharge. The causes of death were not studied.

DISCUSSION

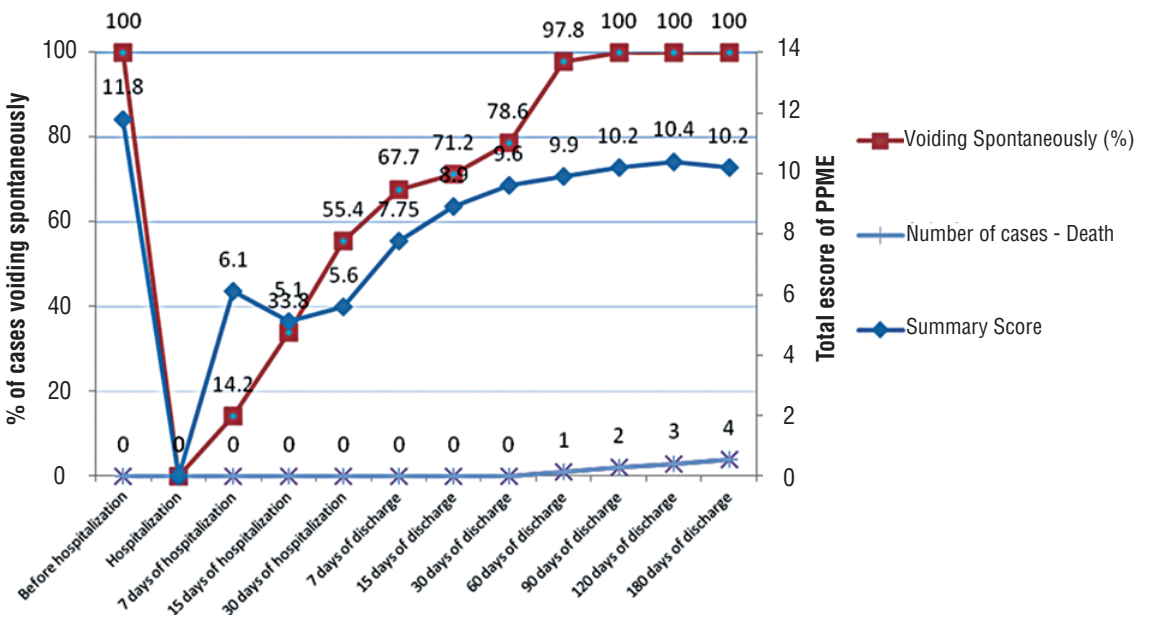
Half of all hospital beds are occupied by people >65 years of age, and it is expected that this demand will increase to 70% by 2050 (4).

Geriatric syndromes, including dementia, polypharmacy, falls, incontinence, pressure ulcers, sensory impairment, and malnutrition (5), are clinical representations of multifactorial etiologies and are associated with an increased risk for adverse outcomes. Functional limitations limit survival and decisively contribute to frailty (6).

Frail individuals often have immobility, gait abnormalities, muscle weakness and poor balance (7). They may have difficulty performing activities of daily living (ADL) and instrumental activities of daily living (IADLs), which are critical to maintaining function.

The functional independence of older people is an indicator of their health status, and diminished independence in hospitalized older people is associated with an increased risk of care burden, mortality and healthcare costs after discharge (1, 8). Whatever the cause, any hospitalization event increases morbidity due to necessary or circumstantial immobilization in bed, promoting patient functional decline during the hospitalization period (9).

Figure 4 - Evolution of recovery for spontaneous voiding matched to PPME index.



Among the problems acquired during immobilization, urinary retention is an undesirable side effect. It is difficult to manage and shows an unpredictable pattern of recovery, frequently extending the period of hospitalization and secondarily aggravating frailty.

Furthermore, the prolonged or necessary use of a urethral catheter reflects the need for third-party assistance, increased costs or the family's insecurity in taking the patient home.

Validated instruments for the measurement of the clinometric properties of mobility in hospitalized older acute medical patients may present floor or ceiling effects.

In this regard, Timed Up and Go (TUG) (10), Functional Ambulation Classification (FAC) (11) and the Barthel Index (BI) (12) were focused on mobility, but they presented limitations in acutely hospitalized patients.

Although PPME was not tested in older acute medical patients, it captured a minimal clinically important difference, presented none of the previously mentioned restrictions, was not greatly influenced by mood or mental status, reflected only the patient's dependency on mobility, and was performed easily and quickly by staff with no special training (13).

The reasons that urinary retention developed in frail older adults cannot be ascertained for certain as it may result from a wide range of physical and cognitive abilities (14, 15). As we often observe AUR in the hospital setting with no urological cause, we hypothesized that resting in bed might result in low neuronal output activities from the same sacral roots as the bladder and lower limbs, which can be clinically measured with tasks for the lower limbs.

Transtibial Electrical Nerve Stimulation (TENS) produced an inhibitory effect on overactive bladder, revealing the linkage between lower limb nerves and pelvic functions (16). Therefore, resuming spontaneous voiding could be measured by lower limb refunctionalization, which may reflect the functionality of the internal pelvis. Our study confirms this assertion, showing a clear relationship between both functions. The empirical observation of AUR as a frequent but transient complication after hernioplasty with no clear reason reinforces this assumption (17).

Hip fracture surgery is a comparable clinical situation. Patients with bed rest present a higher incidence of AUR, which can be reversed by earlier patient mobilization and intermittent catheterization with a return to spontaneous voiding in 5.1 days compared to 9.4 if an indwelling catheter was inserted (18); all patient's voiding was fully restored within 3 months (19).

This may explain why after 7 days of hospitalization, patients are impaired in their mobility scale, although the rate of recovery of spontaneous voiding improves, revealing that the CIC regimen is a powerful stimulus in restoring bladder function.

We assumed that voiding and PPME was normal based on retrospective interviews with the patient or their caregiver as the PPME score was at its maximum before hospitalization. Although we recognize that this could be a flaw in our assumptions, Covinsky et al. (20) also observed that retrospective evaluation is reliable. The main factor evaluated in this study was secondary AUR and its evolution as it relates to the mobility index ranked by PPME.

As previously studied, interventional measures in acutely ill patients to improve mobility scale reduce the length of the hospital stay (12), and all domains of these parameters were clearly improved in staggered fashion after the patients were discharged home.

One limitation may be the fact that urinary residual volume was not measured, but some authors demonstrated no relationship between PVR and improvement in mobility in a rehabilitation ward for older adults (21).

As previously mentioned, hospitalization may decrease lower body function as early as the second day (1), which could also be seen in our population from the severe decrease in mobilization and voiding capacity measured by PPME.

The recovery of lower limb function as measured by the various domains of PPME returned staggeringly and progressively on the days immediately after departure from the ICU, but with recognized impairment if the hospitalization extended beyond 7 days. This is in accordance with the results of studies showing lower body function as a basic indicator of health and recovery in older people (22), which tends to normalize by discharge (23), as was observed at home.

Patients were discharged into the community, abiding by the country's cultural and socioeconomic realities. We do recognize that discharged patients who require care-givers are frequently sent to nursing homes, but one of the strengths of our study is the observational nature of spontaneous recovery in home settings with few interventions because discharge from hospitals rarely involves nursing homes as it does in the United States. In this regard, our study showed new improvement in mobility indexes after 7 days at home in a continuum of the recovery of spontaneous voiding, possibly suggesting that aside from the greater clinical improvement in the primary disease, returning to the familiar environment may contribute to more frequent and a wider amplitude of movements than those of the restrictive hospital environment. We also observed only a partial recovery of the lower limbs, confirming the results of other studies in which 30% of patients treated for acute illness lost the ability to perform ADL compared to pre-admission levels (8). This observation highlights frailty, as demonstrated by the death rate over 180 days, reaffirming that lower mobility scores at baseline tests predict further aggravation of disability (24). The major finding of this study was that leg power measured by a validated instrument is a significant predictor of physical performance (25).

Despite the importance of our results, our study has limitations worthy of discussion as the relative heterogeneity of the studied population limits the generalizability of the results.

CONCLUSIONS

Measuring the recovery of leg function by a simple validated instrument can reflect the recovery rate of spontaneous voiding after AUR due to non-urological causes. We hypothesize that there may be an overlap between the neural sacral roots responsible for bladder function and lower limb functions.

CONFLICT OF INTEREST

None declared.

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The amount of spermatic cord rotation magnifies the time-related orchidectomy risk in Intravaginal testicular torsion

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ABSTRACT

Purpose: To investigate the roles of age, testicular rotation and time in the surgical outcome of intravaginal testicular torsion (iTT).
Patients and Methods: We retrieved the records of all iTT patients treated in our unit from January 2012 to January 2014. Explanatory variables were: age (years); presentation delay (PrD, time between symptoms and hospitalization); surgical delay (SurgD, time between hospitalization and surgery) and testicular rotation (rotation), with surgical outcome (orchidopexy, orchidectomy) as response variable. Differences in PrD, SurgD, age and rotation by surgical outcome were evaluated non-parametrically. Step-down logistic regression included age, PrD, SurgD and rotation as predictors. Statistical significance and confidence intervals (CI) were set at $p<0.05$ and 0.95. Odds ratios (OR) were computed from the model's coefficients.
Results: Complete variable information was available for 117 patients, and most (61, 52.1%) underwent orchidectomy. Ages were similar between orchidectomy and orchidopexy patients (median 15.8 vs. 16.0 years, $p=0.78$). In contrast, PrD (85.0 vs. 8.4 hours, $p<0.001$), SurgD (3.0 vs. 16.0 hours, $p<0.001$) were different between orchidectomy and orchidopexy patients. SurgD was similar with PrD<24 hours (4.0 vs. 2.8, $p=0.1$). Orchidectomy patients had greater rotation (3.0π vs. 2.0π radians, $p<0.001$). Logistic regression revealed that PrD (OR 0.94; 0.92–0.97; $p<0.001$) and rotation (OR 0.43; 0.27–0.70; $p<0.001$) were inversely associated with orchidopexy.
Conclusion: Testicular rotation exerts a multiplicative effect on PrD, so time should not be regarded as the sole predictor of surgical outcome in iTT.

ARTICLE INFO

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INTRODUCTION

Intravaginal testicular torsion (iTT) is a genuine surgical emergency, affecting mainly adolescents and young adults. After a few hours, ischemic injury leads to testicular necrosis or atrophy. In order to reduce organ loss, the time between the beginning of symptoms and treatment must be reduced.

The importance of swift treatment for iTT has been recognized for more than a century. Nash, in 1893, was able to salvage a testicle by timely intervention (1). Three decades later, Thorek (2) noted that, in both of his cases, the organ would have been saved had immediate surgery been undertaken. Fortunately, testicular salvage rates have been improving, although not everywhere

(3, 4). Moreover, it is not unusual to see testicular necrosis with short duration of symptoms, suggesting that the outcome of iTT is not exclusively governed by the duration of ischemia.

One candidate risk factor is the testicular rotation, i.e., the number of turns of the spermatic cord, that appears to damage the organ in a dose-dependent manner: more turns, more vascular occlusion, more ischemia (5, 6). Age is also cited as another risk factor, but reports diverge as to which ages are at increased risk. A worse prognosis associated with younger ages has been attributed to difficulties in communicating symptoms, and to reliance in potentially misleading clinical diagnosis (7–9). On the other hand, older patients were reported to have worse outcomes by holding up to seek medical attention, as well as to diagnostic delays due to the perception that iTT is rare in older adults (10–12).

We found ourselves in a favorable position to investigate the influence of these additional risk factors on the outcome of iTT. Our case load is maximized by the referral of all patients suspected of iTT in our region, a result of the continuous presence of an urologist in our emergency department. Hence, we expect to, with the use of multivariate logistic regression, understand the relationship between ischemia time, testicular rotation and age in the surgical outcome of iTT.

PATIENTS AND METHODS

Data collection and definition of variables

Following institutional review board approval, we retrieved the medical records of all patients surgically treated for iTT from January 1, 2012 to January 31, 2014. Recovered data included: the patient's ages; date and time of symptoms, as well as date and time of urological examination and operation, as date-time variables; the number of turns (rotation) taken by the testicle, as quantified by the surgeon at operation, in π radians (1.0π radian=180°); and surgical outcome (binary: orchidectomy or orchidopexy). The decision to remove the organ was taken by the surgeon if, after surgical detorsion and placement of the organ at a saline bath at 37^oC for at least 20 minutes, no bright red arterial parenchymal bleeding was seen following a stab incision of the tunica albuginea. Only intravaginal torsion cases were included.

Presentation delay (PrD) was calculated subtracting date and time of surgery from date and time of symptom's onset. Surgical waiting times, or surgical delay (SurgD) was calculated as the difference between date and time of hospitalization and date and time of surgery. Treatment delay (TrD) equaled the arithmetic sum of presentation and surgical delays. All variables were included in an electronic spreadsheet for statistical analysis.

Statistical analysis

We first tested for differences in the explanatory variables according to surgical outcome: orchidectomy or orchidopexy. The second stage of the analysis involved multivariate logistic regression. We also studied SurgD in the subset of patients with PrD less than 24 hours, as, by our unit's treatment algorithm, patients examined within 24 hours are offered immediate surgery, whereas those with later presentation are first examined with Doppler ultrasound, and offered surgery if results indicate iTT. All analysis was conducted with the R Statistical Language, version 3.2.3 (13) and its package rms (14). Statistical significance was established at $p<0.05$ and confidence intervals (CI) at 0.95.

Non-parametric analysis

The explanatory variables age, TrD, PrD, SurgD, and rotation did not distribute normally, so differences were evaluated with the Mann–Whitney test. Also, because of non-normalcy of distributions, the relationship between age and PrD was studied with Kendall's rank-based correlation test.

Logistic regression

Backwards step-down logistic regression, removing all cases with missing values, included, initially, the main effects of the predictor variables: Age, PrD, SurgD and rotation, as well as the 2–way interactions: PrD x rotation and SurgD x rotation. We did not include TrD in the initial model, since it is the linear combination of PrD and SurgD. The minimal adequate model was selected

with Akaike's Information Criteria (AIC). Probabilities, odds ratios (OR) and relative odds ratios (ROR) were computed from the final model's coefficients. Confidence intervals and statistical significance for model parameters, probabilities, OR and ROR were also established at 0.95 and at p<0.05.

RESULTS

We identified a total of 142 iTT patients, most of them adolescents (median age 15.8 years, IQR 4.7 years). Median SurgD equaled 5.0 hours, contrasting with a median PrD of 24.5 hours (Table-1). In 25 cases we could not recover information on rotation, so analysis involving this variable was performed on the remaining 117 cases. Overall, 75 patients (52.8%) underwent orchidectomy.

and SurgD (median 14.0 vs. 2.7 hours, p < 0.001), were also significantly longer in patients with lost testicles. SurgD was significantly different between patients with PrD shorter or longer than 24 hours (median 2.7 vs 19.0 hours, p < 0.001). However, among patients presenting before 24 hours of symptoms, SurgD was not significantly different between orchidectomy and orchidopexy cases (median 4.0 vs 2.5 hours, p = 0.1; Figure-3). Twelve patients presenting before 24 hours underwent orchidectomy, including a case with PrD shorter than 4 hours. In contrast, 10 patients with PrD longer than 24 hours had their testicles preserved, including a patient symptomatic for 100 hours.

Rotation

Among the 117 patients analyzed, 61 (52.1%) underwent orchidectomy and 56 (47.9%) orchidopexy. Ages, PrD and SurgD had a similar

Table 1 - Overall results.

N = 142	Median	Range	IQR
Age (years)	15.8	8.1 – 42.3	4.7
PrD (hours)	24.5	1.1 – 609.0	77.0
SurgD (hours)	5.4	0.5 – 145.5	18.0
TrD (hours)	30.0	2.83 – 681.0	101.5
N = 117			
Rotation (π radians)	2.0	0.0 – 6.0	1.0

PrD = presentation delay; **SurgD =** surgical delay; **TrD =** treatment delay; **Rotation =** testicular rotation; **IQR =** interquartile range

BIVARIATE ANALYSIS

Age

Age was not significantly different between patients with patients undergoing orchidectomy or orchidopexy (15.7 vs. 15.8 years, p=0.89, Figure-1, Table-2). Also, there was no correlation between age and PrD (Kendall's tau=-0.02, p=0.76).

Treatment delay

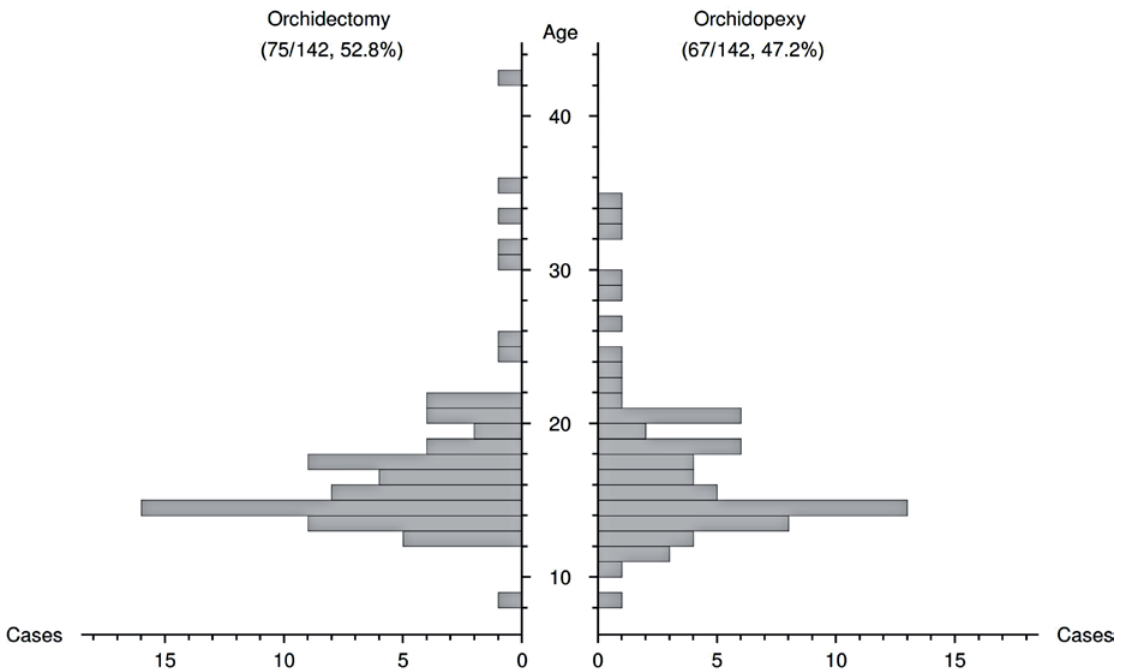
TrD was significantly longer in patients that underwent orchidectomy (median 101.5 vs. 10.5 hours, p < 0.001). Both components of TrD: PrD (median 79.5 vs. 8.0 hours, p < 0.001, Figure-2)

distribution when compared with the full dataset (Table-2), but rotation was significantly different between patients submitted to orchidectomy or orchidopexy (median 3.0π vs. 2.0π radians, p < 0.001, Figure-4). All patients with rotation greater than 5.0π radians underwent orchidectomy, whereas all patients with less than 2.0π radians had their testicles surgically salvaged.

Logistic regression

The minimal adequate model included only PrD (z = -4.64, p < 0.001) and rotation (z = - 3.41, p < 0.001) as adverse predictors of surgical outcome (Table-3, Figure-4). Rotation decreased

Figure 1 - Age distribution of patients either submitted to orchidopexy or orchidectomy.



the likelihood of orchidopexy after controlling for PrD. The ROR for orchidectomy with an increasing rotation of 1.0π to 2.0π radians, with PrD fixed at 6 hours, equaled 2.30 (CI 1.42 – 3.10), whereas the ROR increasing PrD from 6 to 12 hours with a 2.0π radians rotation was computed at 1.43 (1.23 – 1.66). Table-4 contains the probabilities of orchidopexy according to PrD and rotation, computed from the fitted model.

DISCUSSION

We observed an overall low surgical salvage rate (47.2%) with rather long TrD and PrD, reiterating that time is key when treating testicular torsion, for prolonged ischemia times are unequivocally associated with disappointing salvage rates (3, 15, 16). Limited knowledge of this fact may partially explain the 10% salvage rate often seen until 40 years ago (17), and, thankfully, there has been a trend towards better salvage rates in the last decades. Williams (18), in 1979, salvaged 69% of his cases, and Jones (7), in 1986, 75%. The best salvage rate so far recorded, 97.6%, comes from Ireland (19), even though at a cost of a 52.9% false-positive rate. A noteworthy example of diagnostic shrewdness can be seen in the work of Sparks (20), from Rugby, England, presenting a 96% salvage rate as early as 1972.

Delays in treating testicular torsion are sometimes attributed to the lack of diagnostic acumen of emergency department staff, which can lead to medico-legal consequences. However, such argumentation overlooks the fact that treatment delays have two main components: the time interval between the beginning of symptoms and evaluation by the final assistant physician, and the interval between clinical evaluation and treatment itself. We were able to see that, in our population, the time before urological evaluation (presentation delay, PrD) was the dominant component of the delay in treatment. Elsewhere, there are examples that the responsibility for treatment delay may not lie solely with the emergency department staff, which can, point-of-fact, attain high diagnostic accuracy (6, 7, 21). Investigators from California noted that patients' transfers from primary and secondary to tertiary facilities was an independent risk factor for orchidectomy (22). In addition, an English study (15) revealed that caregivers waited in average 32 hours (range 3–240

Table 2 - Bivariate analysis.

		Overall	Orchidectomy	Orchidopexy	P (MW)
N		142	75 (52,8%)	67 (47,2%)	
Age (years)	Range	8.0 – 42.3	8.0 – 42.3	8.8 – 34.6	0.965
	Median (IQR)	15.8 (4.7)	15.7 (4.6)	15.8 (5.9)	
PrD (hours)	Range	1.1 – 609	3.2 – 609.0	1.1 – 100.0	<0.001
	Median (IQR)	24.5 (77.0)	79.5 (110.8)	8.0 (8.4)	
SurgD (hours)	Range	0.5 – 146.0	0.5 – 146.0	0.5 – 51.0	<0.001
	Median (IQR)	5.3 (18.0)	14.0 (24.5)	2.7 (3.0)	
SurgD with PrD < 24 hours	Range	1.0 – 15.5	1.0 – 15.5	1.0 – 10.5	0.176
	Median (IQR)	2.7 (2.5)	4.0 (2.2)	2.5 (2.5)	
N		117	61	56	
Rotation (π radians)	Range	0.0 – 6.0	1.0 – 6.0	0.0 – 5.0	<0.001
	Median (IQR)	2.0 (1.0)	3.0 (2.0)	2.0 (1.0)	
Age (years)	Range	8.1 – 42.3	8.1 – 42.3	8.9 – 34.6	0.773
	Median (IQR)	15.9 (5.6)	15.8 (4.4)	16.0 (5.8)	
PrD (hours)	Range	1.1 – 609.0	3.2 – 609.0	1.1 – 100.0	<0.001
	Median (IQR)	25.8 (80.9)	85.0 (113.0)	8.4 (10.5)	
SurgD (hours)	Range	0.5 – 114.0	0.5 – 114.0	0.5 – 51.0	<0.001
	Median (IQR)	5.8 (19.3)	16.0 (25.0)	3.0 (3.2)	
SurgD with PrD < 24 hours	Range	1.0 – 10.5	1.0 – 5.7	1.0 – 10.5	0.688
	Median (IQR)	2.9 (2.9)	4.0 (2.0)	2.8 (2.5)	

Upper part of the table with **N** = 142, full dataset; lower part of the table with **N** = 117, dataset with complete variable information.
IQR = interquartile range; **PrD** = presentation delay; **SurgD** = surgical delay; **Rotation** = testicular rotation; **MW** = Mann–Whitney's test.

hours) to bring a patient with acute scrotum to medical attention. This extended time was claimed to be responsible for their 45% salvage rate.

There is disagreement about the role of age in the prognosis of testicular torsion. One can find evidence attributing worse prognosis to younger (7–9, 23), older (10–12), as well as to patients at extremes of age, i.e., younger than 10 and older than 40 years (22). We, however, were unable to find any relationship between surgical testicular salvage and age, in both bivariate and logistic regression analysis. Therefore, among the subjects of our study, age did not influence surgical outcome.

In contrast, testicular rotation appears to play an important role in surgical outcome. The existence of some relationship between the amount of rotation, duration of ischemia and surgical outcome has been known for almost a century (2). There is experimental evidence (24) that 3 or 4 complete turns produce irreversible ischemic changes as early as 2 hours, whereas one turn can

Figure 2 - Distribution of presentation delay between patients either submitted to orchidectomy or orchidopexy.

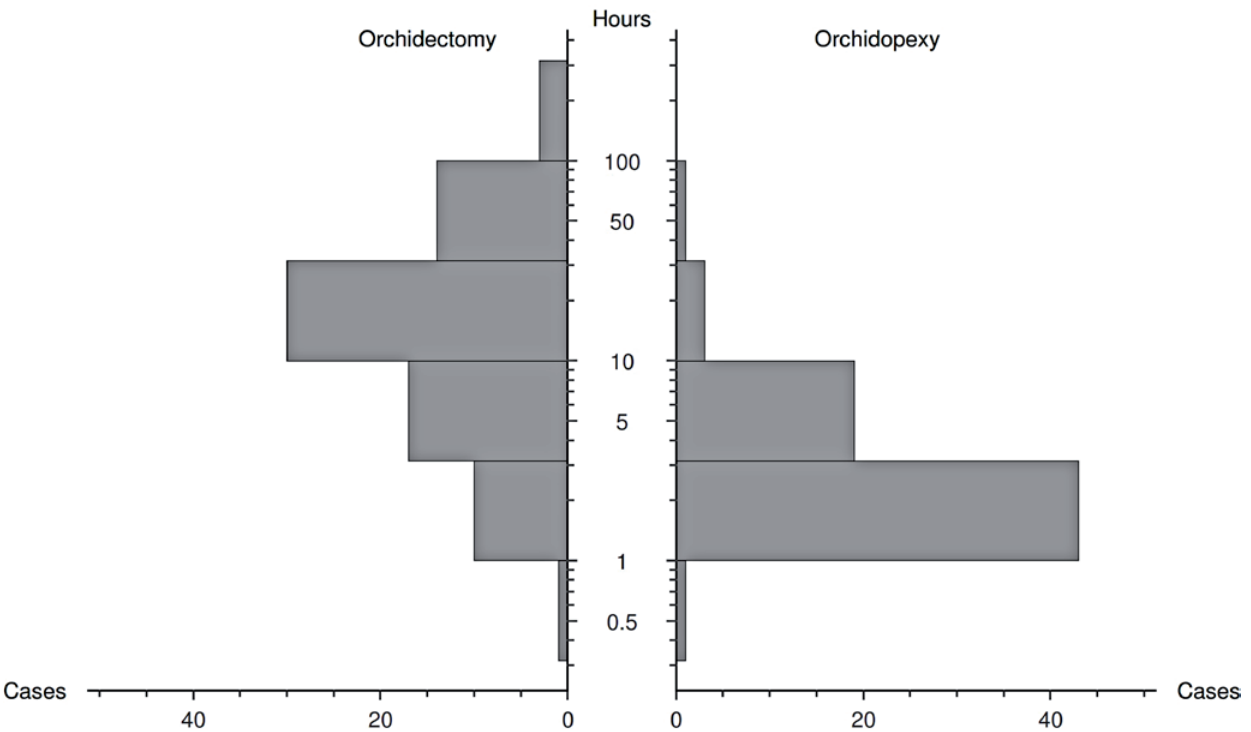
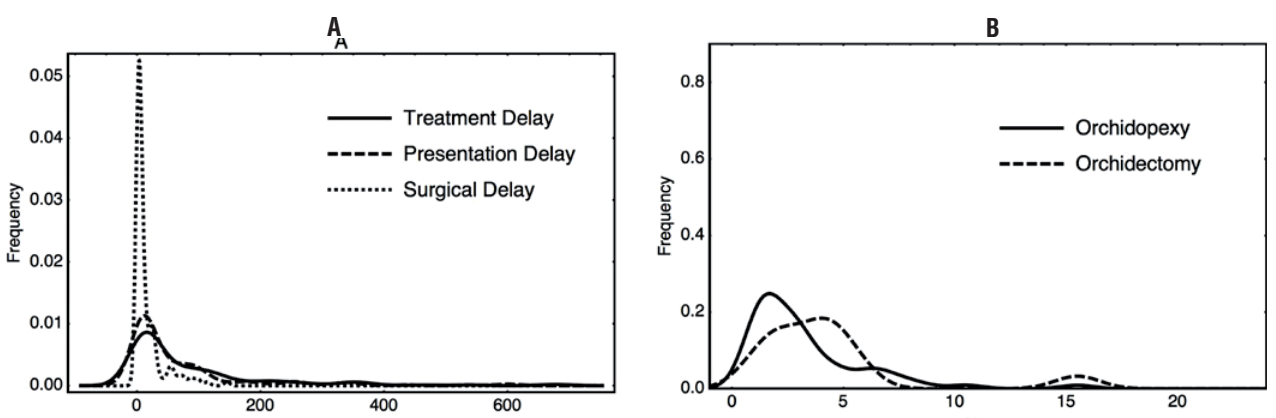


Figure 3 - A: Distribution of treatment, presentation and surgical delay among all patients; B: Distribution of surgical delay between patients either submitted to orchidectomy or orchidopexy, with presentation delay < 24 hours



be tolerated for 12 hours, even though infarction inevitably occurs after 24 hours. Williamson asserted that there is no absolute time beyond which one can assume that infarction is inevitable (6). In his study, one organ was found necrotic after only 4 hours' ischemia, and 2 testicles were viable after 25 days of symptoms. In an analysis of 186 testicular torsion cases, Sessions (25) observed that salvaged testis twisted less than lost organs (360º vs. 540º). Despite the impressive number of cases, the data was not submitted to multivariate analysis, so the relative prognostic significance of time and magnitude of torsion was not investigated. A similar relationship was found by Cummings, that observed that mean rotation in salvaged cases was 412º, contrasting with 630º in non-viable testicles

Figure 4 - Differences in the magnitude of torsion (Rotation, in π radian) between patients either submitted to orchidectomy or orchidopexy.

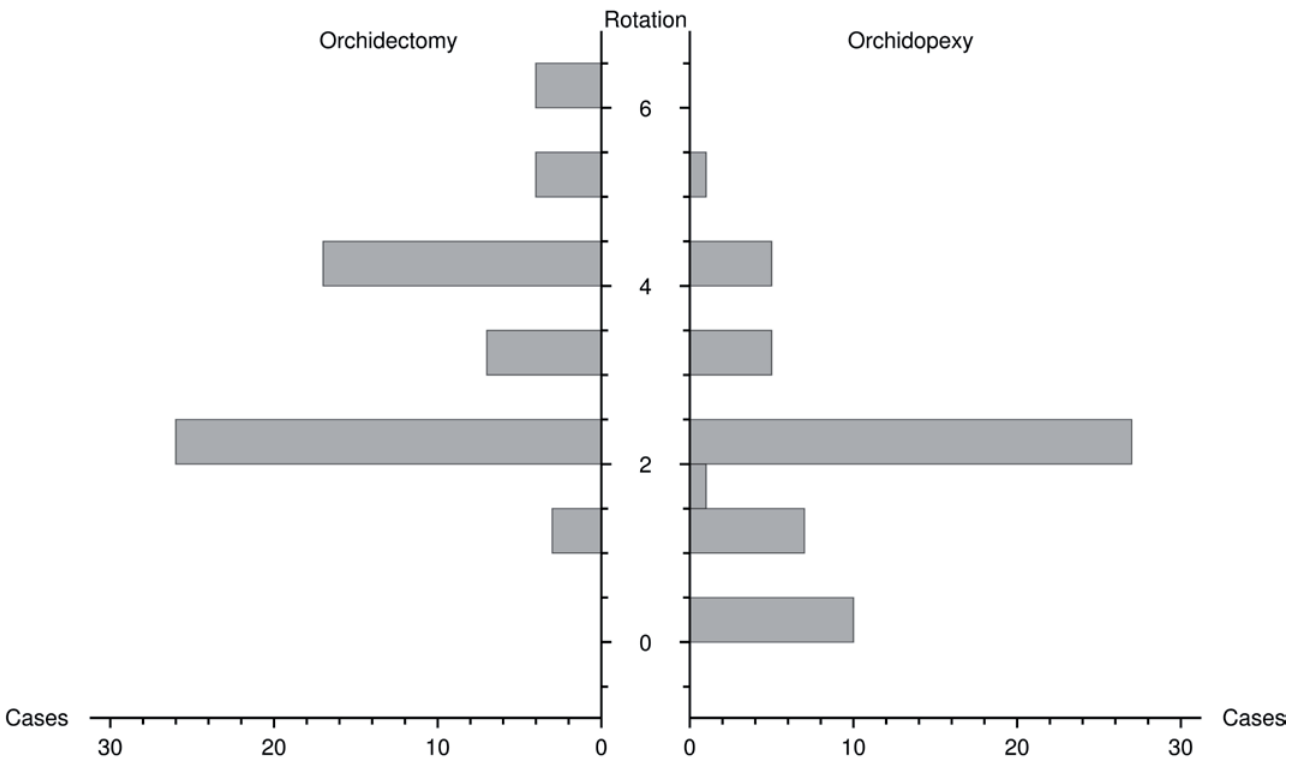


Table 3 - Results of multivariate logistic regression.

Parameter	Estimate (CI)	SE	OR (CI)	P
1	4.19 (2.57, 5.82)	0.83	-	<0.001
PrD (hour)	-0.06 (-0.08, -0.03)	0.01	0.94 (0.92, 0.97)	<0.001
Rotation (π radian)	-0.83 (-1.31, -0.35)	0.24	0.43 (0.27, 0.70)	<0.001

SE = standard error; **CI95** = 0.95 confidence interval; **OR** = odds ratio for testicular salvage, by increasing the explanatory variables by one unit; **PrD** = presentation delay in hours; rotation, magnitude of rotation, in complete turns.

(11). From Kuwait, Al-Hunayan (26) was able to salvage 2 organs after 48 hours of ischemia, and noted that both had less one turn. Tryfonas (27), following 25 of his 75 treated cases, noticed that if rotation was greater than 360º, atrophy ensued after only 4 hours, in a manner similar to what occurred in all cases with ischemia lasting for more than 24 hours. He also noticed no later atrophy between 12 and 24 hours with rotations between 180º and 360º. In a study from China (4), median rotation in salvaged organs was significantly less than in lost organs: 360º (90º–540º) vs. 540º (90º – 960º) (r = - 0.953, p = 0.011). These investigators called attention to 4 orchidectomy cases with less than 6 hours of symptoms, all of which had greater then 720º rotation. In our analysis, both presentation delay and rotation were significantly and independently associated with greater

Table 4 - Probabilities of testicular salvage, computed from the model.

	PrD (hours)		
Rotation (π radians)	6	12	24
1	0.953 (0.718, 0.995)	0.934 (0.605, 0.994)	0.874 (0.358, 0.990)
2	0.898 (0.450, 0.993)	0.860 (0.331, 0.991)	0.751 (0.152, 0.986)
4	0.624 (0.078, 0.995)	0.538 (0.049, 0.982)	0.363 (0.018, 0.973)

Probability (with 0.95 confidence intervals).
PrD = presentation delay; Rotation, magnitude of rotation of the spermatic cord.

orchidectomy rates in iTT. Rotation had a crucial influence in surgical outcome, lowering the probability of orchidopexy even with very short treatment delays, in a dose–dependent manner.

The first consequence of our findings is that one has to deal with greater uncertainty in forecasting surgical testicular salvage in iTT, even with short treatment delays, since it is impossible to know the cord's rotation beforehand. Therefore, diagnostic imaging may not be affordable, for even minimal increases in treatment delay can cost dearly. One might, nevertheless, institute measures to reduce testicular ischemia, such as manual detorsion: manual detorsion can be successful even when converting a 4.0π radian to a 2.0π radian torsion, which could allow some testicular perfusion. Furthermore, there is some experimental evidence that ischemic injury can be reduced with local hypothermia (28, 29), a very simple measure. There is ongoing research on pharmacological therapy to reduce ischemic injury (30), but the possibility of serious adverse effects requires careful clinical consideration.

The second consequence is that surgical treatment should not be withheld with the argument that the testicle is all but lost, even in patients with long delays in presentation (>24 hours). Ten of our patients (7%) in such situation had their testicles surgically salvaged, including one with 100 hours of symptoms. One should keep in mind that patients with a single twist of the spermatic cord might preserve some testicular irrigation, and have a viable testis at surgical exploration. Moreover, the patient might be suffering from intermittent torsion, which explains finding a non-rotated testicle, even if typical symptoms are present.

This study has several drawbacks worth mentioning. The response variable of our analysis was surgical outcome, which is not the same as treatment outcome. Treatment outcomes will be most likely worse than surgical outcomes, since some surgically salvaged organs will eventually atrophy. Thus, even with our low surgical salvage rates, our results might have represented an optimistic scenario. Regarding our logistic model, we included rotation as a continuous variable, even though it was recorded at discrete intervals. On the other hand, the rotation of the cord must occur continuously: a 4.0π radian rotation has necessarily gone through lesser degrees, and, indeed, can be medically or spontaneously converted to a lesser degree. Furthermore, we also acknowledge the possibility of a non-linear effect of rotation on testicular perfusion, and recommend additional caution in the interpretation of the regression results. Lastly, we also did not have access to data on patient referrals and prior treatments, *e.g.*, manual detorsion, so the use of treatment delay and its components as a surrogate for the duration of ischemia might be negatively biased.

CONCLUSIONS

We have demonstrated, with non-parametric and multivariate logistic regression analysis, that both presentation delay, the dominant component of treatment delay for testicular torsion in our population, and testicular rotation were independently and inversely associated with surgical salvage in intravaginal testicular torsion. Most importantly, that testicular rotation exerts a multiplicative effect on ischemia time.

The exclusion of other causes of acute scrotum by imaging studies is currently accepted practice, provided surgery is not postponed. However, our results demonstrate that this might be a dangerous path, for there seems to be no safe period in intravaginal testicular torsion.

ABBREVIATIONS

TrD = Treatment Delay
PrD = Presentation Delay
SurgD = Surgical Delay
iTT = Intravaginal Testicular Torsion
CI = 0.95 Confidence Interval
OR = Odds Ratio
ROR = Relative Odds Ratio
IQR = Interquartile Range
AIC = Akaike's Information Criterion

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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A wet dressing for male genital surgery: A phase II clinical trial

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ABSTRACT

Purpose: This study was to confirm the safety and efficacy of BC dressing when used in surgical male wound healing at the urogenital area.
Methods: Open, non-controlled clinical study of phase II. A total of 141 patients, among those children, adolescents and adults with hypospadias (112), epispadias (04), phymosis (13) and Peyronie's disease (12) that had a BC dressing applied over the operated area after surgery. A written informed consent was obtained from all participants. Study exclusion criteria were patients with other alternative treatment indications due to the severity, extent of the injury or the underlying disease. The outcomes evaluated were efficacy, safe and complete healing. The costs were discussed.
Results: In 68% patients, the BC dressing fell off spontaneously. The BC was removed without complications in 13% of patients at the outpatient clinic during the follow-up visit and 17% not reported the time of removal. In 3% of the cases, the dressing fell off early. Complete healing was observed between 8th and 10th days after surgery. The BC dressings have shown a good tolerance by all the patients and there were no reports of serious adverse events.
Conclusion: The bacterial cellulose dressings have shown efficacy, safety and that can be considered as a satisfactory alternative for postoperative wound healing in urogenital area and with low cost.

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Keywords:
Safety; Surgical Procedures, Operative; Genitalia, Male

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INTRODUCTION

Surgical correction of genitalia anomalies has evolved recently with the use of new techniques, instruments and sutures, which have contributed to better results. In spite of this, the correct choice of dressing is still challenging, because wound healing is a dynamic and complex phenomenon and its phase duration in the urogenital area is longer when compared to dermatological healing. A number of materials have been used with different results, but there is no consensus about their use (1-7). Thus, the question remains regarding which dressing is the best for postoperative male wound healing.

The clinical indication of a specific dressing is based upon the protective function and mechanical barrier of the tissues against contamination and reduction of edema caused by the surgical trauma. The material to be used should have physical features including elasticity, resistance and flexibility and must adjust tightly to the tissue surface. The chosen dressing must present minimal adverse reactions when in contact with living tissues or organic fluids and must be easily removable (8, 9).

A bacterial cellulose (BC) dressing is being studied as a viable alternative. Previous studies, phase I, have shown its effectiveness as a mechanical barrier and a safe adjuvant in the treatment of a surgical wound after hypospadias correction. This material showed the following characteristics for an ideal dressing: it removed exudates, created a moist environment, offered protection from foreign substances and promoted tissue regeneration (9).

The objective of this study was to confirm the safety and efficacy of the BC dressing when used in surgical male wound healing in the urogenital area.

MATERIALS AND METHODS

Sample

This was an open, non-controlled clinical trial (Non-Randomized Controlled Trial, NRCT), phase II study, to assess the BC dressing efficacy and safety. Both efficiency and safety were demonstrated in a preview study, phase I (Randomized Controlled Trial, RCT). The phase I study, using polyurethane and BC dressings enabled comparison and exclusion of the polyurethane group, due to better results obtained from the BC dressing in cases of hypospadias repair (9).

The phase ll population study included children, adolescents and adults with hypospadias (112-40% proximal and 60% distal), epispadias [04], phymosis [13] and Peyronie's disease [12]. The patients and their relatives were formally informed about the study and were invited to join it. One hundred and forty-one [141] patients were included in the study after a written informed consent.

Patients were submitted to anamnesis, including questions about previous surgeries, and physical and urological examinations. The exclusion criteria were patients with other alternative treatment indications due to the severity, extent of the injury or due to underlying disease.

Technique of BC dressing application

A physician, with residents participating as assistants, operated on the patients. Immediately after the end of the surgery the BC dressing was applied. To make sure that all procedures were carried out properly, all patients were hospitalized in a public teaching hospital for 10 days for hypospadias or epispadias and 2 days for Peyronie disease. Circumcision patients left the hospital on the same day. The BC dressing, sized 8.0×15.0cm, could be cut according to patient surgical wound size. The BC dressings had been previously sterilized using 25kGy of gamma irradiation. After end of the surgical procedure, the area was washed out with saline and dried with gauze. The dressings were applied over the whole penile shaft excluding glands in all cases. No tension was applied to the wound area when the BC dressing was fixed (9). The BC dressings were donated by the Laboratory of Biopolymers at the Experimental Station of Sugarcane, Federal Rural University of Pernambuco.

Outcomes evaluated

Safety was assessed by adverse event reports, such as skin irritability next to the dressing area, categorized by feeling of warmth, itching, swelling, pain, and hyperemia.

Efficacy was classified according to the degree of adhesion to the wound area (fully adhered, partially detached or without adhesiveness); discomfort (described during the questionnaire as "very uncomfortable", "uncomfortable", or "not a problem" during the BC dressing use); and transudation, evaluated by exudates drainage and the BC dressing ability to remain fixed when wet.

The primary endpoint was the time range needed for complete healing, measured by time at which the BC dressing spontaneously fell off. Other important outcomes such as pain, wound volume reduction, granulation, odor and scar quality were also monitored.

In addition to these parameters, a comparison with other dressings was made in order to estimated costs and relationship of BC to other dressing already available on the market. The comparisons ranged from individual sale price for each dressing to the required number of surgical wound manipulations required in the urogenital area, over the 14 days that the patient was being monitored.

Furthermore, the study also provides a descriptive analysis of phase II data. It compares statistical inference between phases I and II using the Fisher's exact test, considering the nominal level of 0.05 to reject the null hypothesis.

Ethical Aspects

The study followed the ethical recommendations of the National Council of Health, the Helsinki Declaration and the Nuremberg Code for human experiment. The study is also listed on www.clinicaltrials.gov, #NCT02531828, and was approved by the National Ethics Committee in Research (CONEP #676.414). The non-inclusion of a control group was discussed and accepted by the Ethical Committee of the Institution.

RESULTS

Table-1 summarizes the results. The groups ranged in ages from 2 to 12 years old (children), with an average of 5.4 years (hypospadias or epispadias); 12 to 16 years old (adolescents) with an average of 14.7 years (circumcision); and 50 to 60 years old (adults), with an average of 53.6 years (Peyronie's disease).

The follow-up evaluation was done by one of the team members on a daily basis during the time the patients were in hospital. The BC dressing removal was carried out considering the monitoring time previously defined for each case.

The patients and their parents were advised to keep the bandage in situ after hospital discharge and to inform the researchers when the BC dressing fell off spontaneously.

In 66 cases, the dressing fell off spontaneously around the 9th or 10th day during the hospital stay. These patients were part of the hypospadias correction group (Figure-1).

For twenty-nine patients the BC dressing fell off between 11 to 14 days post surgery, with the regular washing instructions having been followed properly. These patients underwent surgery for hypospadias correction, epispadias or phimosis (Figure-2).

Six adult patients submitted to circumcision and all patients treated for Peyronie's disease [12] had their BC dressing removed at the clinic during the follow-up visit, between the 8th and 10th days after surgery. In all cases [18] the operated area was perfectly healed.

Table 1 - Sample characterization and parameters evaluated.

Disease	N	Hospitalization (N days)	Age (average/ years)	Time to Dressing Removal (day)				
				Fell off Spontaneously			Removed	Not Informed
				1st*	9th - 10th	11th - 14th	8th – 10th	
Hypospadias	112	10	5.4	2	66	25	0	19
Epispadias	4			0	0	3	0	1
Phymosis	13	0	14.7	2	0	1	6	4
Peyronie's	12	2	53.6	0	0	0	12	0
Total	**141**	**10**		**4**	**66**	**29**	**18**	**24**
(%)				**3%**	**47%**	**21%**	**13%**	**17%**

Note: N = number. Values are average, total number or percentage (%).
* The dressing was reapplied and remained until 11th day.

Figure 1 - BC dressing molded to the penile shaft, involving all surface.

Figure 2 - BC dressing fell off spontaneously, after complete healing.

The exact time of spontaneous falling of the dressing was not reported for twenty four (17%) patients, but all of them were evaluated during the follow-up visit and a satisfactory outcome was observed.

In four patients (2 phymosis, 2 hypospadias) the BC dressing fell off spontaneously on the first postoperative day without further complications except edema. In those cases, the dressing was reapplied and remained until the 11th day. The BC dressings were well tolerated by all patients. BC efficacy and safety in all cases are summarized in Table-2. Hyperemia limited to the dressing area, but without edema or other local irritation signs was observed in five patients.

Most of the patients suffered discomfort (62.4%); some of them (37.6%) said that the BC dressing presence even reduced the pain. Analgesic was prescribed to approximately 50% of the patients on the first day after surgery and this dropped to 30% on the following days. Besides that, there was no analgesic indication for use during the BC dressing removal.

Clinical complications were not observed (such as ischemia, impeded voiding, penile chordee and infection). The professionals who accompanied the BC dressing and the wound healing process classified the odor and exudate as sui generis.

DISCUSSION

Numerous variations in the type and style of dressings have been proposed (10-12). There is no consensus on the correct dressing material to be used during the post-operatory period of male patients with genital anomalies. However, an ideal wound dressing must be easily and quickly applied, it must effectively absorb the leakages of the wound, pressurize the flaps and grafts effectively, without damaging blood circulation, thus preventing hematoma formation and helping wound healing, it must protect against infections, and must be easily and painlessly removable (1, 12).

In the present study, there was no need for dressing exchange and it was possible to wash as many times as needed, including the daily bath. The BC dressing is multiperforated and transparent making it possible for caretakers and doctors to discern the existence of possible hematomas or necrosis areas which are very troublesome in male genitalia surgeries. The BC dressing adheres naturally to the wound due to its hygroscopic characteristics, providing protection to the injured area. During the wound reepithelialization the BC dressing usually starts to come off after a couple of days and falls off spontaneously when complete healing is achieved. This dressing is effective in odor control, in exudation capacity, in humidity and temperature maintenance, all required for surgical wound healing. These characteristics were similar to those in the Phase I study (9).

BC is a biomaterial, obtained by bacterial synthesis from sugarcane molasses (13), described in previous studies as a safe dressing with low toxicity (14), biocompatible (15), promoting growth and cell differentiation (17) and, thus, contributing to the healing process (9, 16, 17) and epithelialization (18). Preclinical and clinical studies have shown that this biomaterial is effective as a mechanical barrier and adjuvant in the treatment of surgical wounds (9) and in ulcerative injuries (17).

The BC dressing is easy to use (applied/removed) and during the present study no difficulty was reported in carrying out routine hygiene procedures. Caretakers, patients and doctors also described the BC as easy to remove after saline solution (0.9%) or water irrigation. On the other hand, in a previous study that had a control group using polyurethane as a dressing, three patients (10%) reported difficulty during dressing removal due to its strong adhesion, the process as being stressful and their need for analgesics (9).

In comparison, the polyurethane dressing is a plausible alternative, whereas the BC dressing can be named as intelligent (9). The dressing referred to as “intelligent” must be able to alter the wound microenvironment, inducing endogenous signaling and leading to a wound repair (19) such as cytokines and growth factors (20).

A slight hyperemia limited to the surgical scar area was observed during the first three days with no other local irritation signs. The pain and discomfort reported by most patients can be regarded as an individual response and is possibly

Table 2 - Outcomes evaluated in Phase II compared to Phase I Study (unpublished data).

Outcomes		Phase I Study (Hypospadias)		Phase II Study (Hypospadias, Epispadias, Phymosis and Peyronie's Disease)			
		Polyurethane	BC	BC	p-value	RR	IC 95%
	N° of patients	30	30	141	-	-	-
SAFETY	Adverse events:						
	Hyperemia	0	1 (3.3%)	5 (3.6%)	0.6120[a]	1.556	0.8304-2.914
	Hyperemia/Edema	2 (6.7%)	0	0	0.1471[b]	2.264	0.8678-5.906
	Edema	1 (3.3%)	0	0	1.0000[c]	0.9483	0.1537-5.852
EFFICACY	Adherence degree:						
	Fully adhered	30 (100%)	28 (93.3%)	137 (97.2%)	-	-	-
	Partially detached	0	2 (6.7%)	2 (1.4%)	0.4915[a]	-	-
					1.0000[b]	-	-
					0.1453[c]	0.3394	0.1204-0.9571
	Difficulty removed	3 (10%)	0	0	0.2373[a]	2.111	1.606-2.776
					0.0050[b*]	6.222	4.404-8.791
						-	-
	Early dressing fall	0	2 (6.7%)	4 (2.8%)	0.4915[a]	-	-
					1.0000[b]	-	-
					0.3105[c]	0.5419	0.1664-1.765
	Pain and discomfort:						
	Uncomfortable	23 (76.7%)	24 (80%)	88 (62.4%)	1.0000[a]	0.9088	0.5078-1.626
	Not a problem	7 (23.3%)	6 (20%)	53 (37.6%)	0.2054[b]	1.776	0.8095-3.897
					0.0898[c]	2.107	0.9120-4.868
	Use of analgesic:						
	In the 1st p.o.	20 (66.7%)	21 (70%)	70 (49.6%)	1.0000[a]	0.9268	0.5458-1.574
					0.1086[b]	1.800	0.8962-3.615
					0.0463[c*]	2.051	0.9975-4.218
	After 1st p.o.	8 (26.7%)	6 (20%)	20 (14.2%)	0.7611[a]	1.195	0.6928-2.061
					0.1062[b]	1.857	0.9216-3.742
					0.4095[c]	1.394	0.6319-3.076
	At dressing removal	3 (10%)	0	0	0.2373[a]	2.111	1.606-2.776
					0.0050[b*]	6.222	4.404-8.791
					-	-	-
	Healing (time)						
	8th-10th	9 (30%)	22 (73.3%)	84 (59.6%)	0.0017[a*]	0.4009	0.2212-0.7266
	11th-14th	21 (70%)	8 (26.7%)	33 (23.4%)	<0.0001[b*]	0.2488	0.1229-0.5038
					1.0000[c]	1.064	0.5153-2.195

Notes: p.o = postoperative; **BC** = Bacterial Cellulose; **RR** = Relative Risk; **IC** = confidence interval. Values are total number or percentage (%).* Statistical significance if p<0.05, to a: Polyurethane≠BC phase I; **b:** Polyurethane≠BC phase II; **c:** BC phase I≠BC phase II, by the Fisher's exact test.

related to the surgical trauma. However, some patients reported pain relief using the BC dressing (37.6%). There were no reports of any adverse events. Similar BC dressing outcomes data were observed in phase I (9).

The potential disadvantages (such as ischemia, infection and pain during dressing removal) identified in another study (12) were not observed when the BC dressing was used.

This dressing provided effective pressure in hypospadias or epispadias surgery; it was effective in preventing mucosal bleeding after circumcision and provided a perfect healing in Peyronie's disease patients. In most patients, the BC dressing spontaneously fell off (71%) and the healing process was accomplished between 8th and 10th postoperative day (60%).

Although there is still controversy about the need for a post-operative dressing, mainly regarding hypospadias repair (13, 21), in the present study the BC proved to be a satisfactory wound dressing because it removes exudate material, creates a moist environment, offers protection from foreign substances and promotes tissue regeneration (Table-2).

The estimated cost of the BC dressing (US$4 per patient) is low when compared to similar materials (ranging from US$17 to US$25) or others, such as polyurethane (ranging from US$5 to US$7).

CONCLUSIONS

The absence of adverse events confirms BC dressing safety and its efficacy can be validated by the suitable healing time, adhesiveness in the wound area, retention of the moisture, transudation capacity and pain and discomfort relief. The biomaterial is a highly satisfactory alternative, since it is a natural product obtained from renewable source, low cost and its use is adequate for postoperative wound healing in the urogenital area.

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CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Can a graft be placed over a flap in complex hypospadias surgery? An experimental study in rabbits

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ABSTRACT

Purpose: To develop a rabbit experimental study to test the hypothesis that surgical repair of hypospadias with severe ventral curvatures might be completed in one stage, if a graft, such as buccal mucosa, could be placed over the tunica vaginalis flap used in corporoplasty for ventral lengthening, with the addition of an onlay preputial island flap to complete the urethroplasty.
Materials and methods: The experimental procedure with rabbits included a tunica vaginalis flap for reconstruction of the corpora after corporotomy, simulating a ventral lengthening operation. A buccal mucosa graft was placed directly on top of the flap, and the urethroplasty was completed with an onlay preputial island flap. Eight rabbits were divided into 4 groups, sacrificed at 2, 4, 8 and 12 weeks postoperatively, and submitted to histological evaluation.
Results: We observed a large number of complications, such as fistula (75%), urinary retention (50%) and stenosis (50%). There were two deaths related to the procedure. Histological evaluation demonstrated a severe and persistent inflammatory reaction. No viable tunica vaginalis or buccal mucosa was identified.
Conclusions: In this animal model, the association of a buccal mucosa graft over the tunica vaginalis flap was not successful, and resulted in complete loss of both tissues.

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Hypospadias; Urogenital Abnormalities; Urologic Surgical Procedures

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INTRODUCTION

Hypospadia is one of the most common congenital deformities in humans. Its incidence varies between 1:1000 and 1:100 births (1, 2). The etiology is not fully understood, but there are theories involving testosterone deficiency, multifactorial causes, genetic predisposition, tissue remodeling and others (3). The recommended treatment is surgery at between six and twelve months of age (4).

The choice of optimal method depends on anatomical factors, one of the main challenges in surgery for severe hypospadias is the correction of severe ventral curvatures, especially in cases where only a dorsal plication is not sufficient to straighten the penis shaft, and ventral lengthening of the corpus cavernosum is necessary. A number of tissues have been used as grafts to restore corpora integrity after corporotomy; the main ones are the tunica vaginalis flap, the dermal allograft and the porcine intestinal submucosa (5).

We aimed to evaluate histologically in an animal model the hypothesis that surgical repair of hypospadias with severe ventral curvatures

might be completed in one stage, if a graft, such as buccal mucosa, could be placed over the tunica vaginalis flap used in corporoplasty for ventral lengthening, with the addition of an onlay preputial island flap to complete the urethroplasty. The study focuses on assessing the dogma if grafting over a flap tissue is feasible.

MATERIALS AND METHODS

We designed an experimental study approved by the institutional ethical review board. We treated 8 male rabbits of the species Oryctolagus cuniculus from a New Zealand strain, weighing between 2.0kg and 2.5kg. The sample was divided into 4 groups of 2 of animals, according to the date of euthanasia: sacrificed after 2, 4, 6 and 12 weeks.

Surgical technique

We obtained a 1.0 x 0.5cm buccal mucosa graft from the donor jugal area. Using sterile techniques and a 3.5 x optical magnifying glass, the penis was freed by incising the fold between the ventral penile portion and the anus, facilitating access to the urethra. After exposing the urethra, the penile portion of it was completely separated from the corpus cavernosum, exposing the tunica albuginea. The urethra was entirely sectioned transversally, and the urethral stumps were fixed to the corpus cavernosum with 6.0 PDS suture thread, maintaining a distance of 1cm.

The left hemiscrotum (rabbits have two independent hemi scrotum) was incised and the tunica vaginalis separated from the testicle to obtain a flap that could reach the urethra. A subcutaneous tunnel was then created, so that the flap obtained could pass through the tunnel and reach the urethra. The corpus cavernosum exposed by the incision of the urethra was repaired with PDS suture 6.0, to enable repair of a defect in it, by sectioning the tunica albuginea of the corpus cavernosum over an area of 0.5 x 0.5cm, simulating a corporotomy. At this point, there was intense bleeding which was controlled by suturing the tunica vaginalis flap (visceral surface) to the edge of the defect of the corpus cavernosum with PDS 7.0, in continuous form, along three quadrants (upper, lower, and right side), keeping the pedicle of the tunica free (Figure-1). The buccal mucosa graft was then positioned over the tunica vaginalis and sutured with continuous PDS 7.0 stitches, connecting the shorter edges of the graft to the back part of the urethral stumps, thereby reconstructing the urethral plate (Figure-1). A 1.0 x 0.4cm longitudinal flap was then made out of the inner foreskin of the rabbit's penis. For this, two anchor stitches were applied to the inner foreskin, on the ventral surface, 1cm from the boundary between the skin and the mucosa. Thus, the parietal surface of the foreskin was exposed, to comprise the lumen of the future neourethra when laid over the urethral anastomosis (Figure-1). We opted to use a flap of the ventral foreskin, avoiding transposition of the flap from the dorsal to the ventral surface, simplifying and streamlining the procedure. In this way, after defining the flap, it was rotated from distal to proximal, thereby covering the urethral defect, to complete the neo urethroplasty. After rotating the flap, a continuous suture of the neourethra was made with PDS 7.0 thread. Following the urethroplasty, reconstruction of the penile skin was completed with the synthesis of subcutaneous tissue and genital skin, with separate stitches of catgut 4.0. The urethral catheter was withdrawn at the end of the procedure. Neither drains nor cystostomy were used postoperatively.

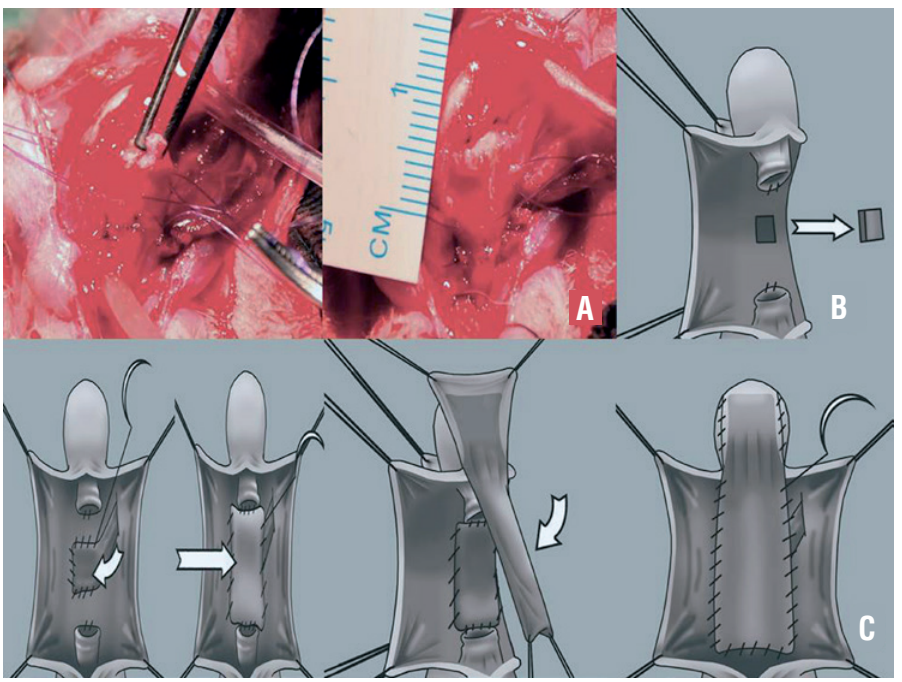
Gross histological analysis

A macroscopic analysis of the rabbit's penis was conducted looking for scar healing, external appearance, and the presence of complications such as fistula or diverticulum. To evaluate the presence of stenosis, the urethra of each animal was catheterized with a urethral tube. The penis was sectioned at its base, preserving the corpora cavernosa and corpus spongiosum, and immediately fixed in 10% formaldehyde for a period up to 20 days.

Microscopic analysis

The pieces were sectioned transversally in 3mm slices, allowing the inclusion of 4 transversal segments of the same penis in each block, which were processed using the normal technique for embedding in paraffin. Slices of whole penis

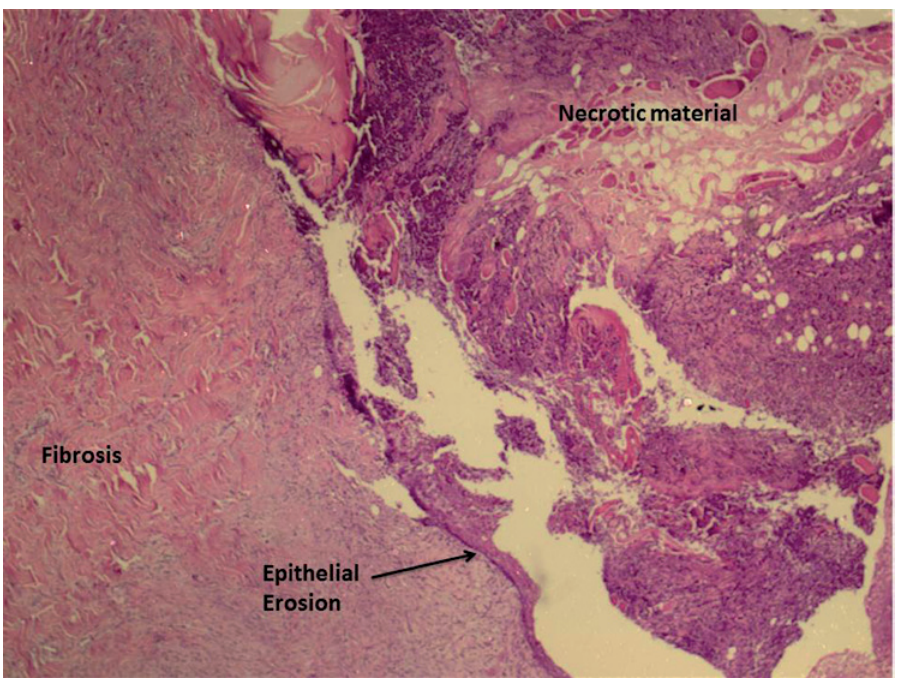
Figure 1 - Step-by-step description of the technique consisting of a tunica vaginalis flap for reconstruction of the corpora after corporotomy. A buccal mucosa graft was placed directly on top of the flap, and the urethroplasty was completed with an onlay preputial island flap.



were included, from the glans, passing through the region that was operated on, to the base, and analyses at 40, 100, and 400 x magnification were performed with an optical microscope (Nikon Eclipse E 600). The paraffin blocks were cut to a thickness of 5 microns, with a rotary paraffin microtome, and stained with hematoxylin eosin (HE) and Masson (TM). A histological evaluation was conducted with an optical microscope by a single pathologist, specialized in the urogenital tract and experienced in the analysis of rabbit urethra (SRRA). The pathologist had no knowledge of the date of euthanasia of each case, and analyzed all the slides on the same day at the end of the study (Figure-2).

The predominant inflammatory phenomena (intensity of acute and chronic inflammation), the presence and intensity of fibrosis, the type of revetment epithelium of the neourethra, and especially, any epithelial changes that occurred postoperatively were evaluated, as well as any complications. An acute inflammatory reaction was defined as the predominant presence of polymorphonuclear leukocytes, and a chronic inflammatory reaction was defined by the predominant presence of lymphoplasmacytic infiltrate. Semiquantitative analysis of the inflammatory reaction was based on the following criteria: a score of zero for the absence of an inflammatory reaction, a score of 1 for minimal inflammation, 2 for moderate inflammation, and 3 for extensive inflammation characterized by abscesses or microabscesses for the acute type, and the presence of aggregations of lymphocytes for the chronic type. Fibrosis was characterized by the presence of fibroblasts replacing normal tissue with collagen deposits, and calculated by the distance between the urethral lumen and the beginning of the corpus cavernosum, using scores of 1 (minimal fibrosis), 2 (moderate), and 3 (maximum). The types of epithelia considered were transitional cell epithelium (urothelium), non-keratinized stratified epithelium (buccal mucosa), and keratinized stratified epithelium (lining of the inner foreskin). The

Figure 2 - Histological aspect of the reconstructed urethra in which dorsal component consisted of a transitional urothelium and ventral component of a stratified scamous epithelium (group 8 weeks, HE x 40).



complications looked for were fistulas, diverticula, stenosis, and dehiscence. The results of the histological analysis of the eight animals are shown as descriptive values and frequencies, and no statistical analysis was performed. There were no missing values to deal with.

RESULTS

In the first postoperative week, intense hyperemia of the surgical wound and scrotal edema were observed in all eight animals. In the pair of animals sacrificed at two weeks, an increase in scrotal edema was noted, with one rabbit presenting necrosis of the scrotal skin, as well as an urethro-cutaneous fistula and inflammation of the surgical site, leading to death. The outcome of the other animal was satisfactory, and euthanasia was performed at 14 days. In the animals in Group 2 (four weeks), the presence of urethra-cutaneous fistula was noted from the second week and persisted until the time of euthanasia. However, an apparent improvement of the scrotal edema was observed.

The presence of fistula was confirmed in both rabbits in Group 3 (eight weeks). One rabbit made good initial progress, but evolved with a voluminous urethra-cutaneous fistula and died at 53 days. The animals in Group 4 (sacrificed at 12 weeks) had good postoperative evolution. One of the animals presented leakage of urine from the proximal edge of the wound during the first week, which stopped spontaneously. The other animal did not have fistula. Catheterization was not possible in four of the six animals with fistula. We consider only two of the animals, one from the 2 week group and one from the 12 week group, to have evolved without complications (Table-1). These animals were evaluated within six hours following the lethal event. Both had moisture in the genital region, indicating the presence of urethra-cutaneous fistula and difficulty inserting the tube. After removing the tube, drainage of a large amount of urine was observed, characteristic of urinary retention caused by stenosis. In the other animals, there were no difficulties with tube insertion.

Table 1 - Description of surgical complications.

Group	Animal	Complications
Group 1 (2 weeks)	Animal 1A	Necrosis of the scrotal skin/ urethrocutaneous fistula/ Death
	Animal 1B	Normal
Group 2 (4 weeks)	Animal 2A	Urethrocutaneous fistula
	Animal 2B	Urethrocutaneous fistula
Group 3 (8 weeks)	Animal 3A	Urethrocutaneous fistula / Death
	Animal 3B	Urethrocutaneous fistula
Group 4 (12 weeks)	Animal 4A	Urethrocutaneous fistula (spontaneous resolution)
	Animal 4B	Normal

Microscopic results

For a better evaluation of microscopic phenomena, the inflammatory findings, fibrosis, characteristics of the epithelium, and characteristics of the chorion are shown in Table-2.

DISCUSSION

Hypospadias repair is a challenging topic of urogenital reconstructive surgery, and many different techniques are currently being used (6). Around 10% of patients with proximal hypospadias have true chordees (7). In our study, we made an ambitious three concept proposal to correct complex hypospadias with: 1) dorsal buccal mucosa graft for replacement urethroplasty, ventral flap of foreskin for the ventral region of the penis and tunica vaginalis flap for corporoplasty; 2) the tunica vaginalis flap overlaying the onlay buccal mucosa graft for the urethroplasty; and 3) all this in a one-stage procedure. Two stage repair is the most commonly used technique in proximal hypospadias or in hypospadias with severe chordee, where it is necessary to section the urethral plate for correction (6, 8, 9). In fact, in cases where it is necessary to perform corporoplasty in addition to plate sectioning, there appears to be a consensus that two stage repair is preferable, with a variety of techniques used for corporoplasty (6). However, the development of a one stage procedure for complex hypospadias is still being investigated (10).

Substitution tissues possibly used in urological surgery are the arteries, veins, the ureter, the cecal appendix, the skin, bladder and buccal mucosa. Tunica vaginalis has been used extensively in surgery for the treatment of Peyronie's disease and chordee (11, 12), in the prevention of fistula and to cover suture stitches. Clinical (13) and experimental studies support the use of tunica vaginalis as a flap for ventral corporoplasty (11, 13) and urethral reconstructions, with one dorsal and one ventral "onlay" flap (14). An experimental study with rabbits comparing the tunica vaginalis as a flap with the same tissue as the graft found that the flap had good integration, but the same was not true for the graft (11). In an experimental study with rabbits in our university (15), the buccal mucosa showed good integration results. Histological results showed no fibrosis, retraction or necrosis in 12 rabbits after 6 weeks. That study inspired us to use buccal mucosa in our experiment. However, while in that study only moderate, acute inflammation was seen, we observed intense inflammation in the whole sample, with ulceration and neutrophil collections in two to four weeks. We attribute this inflammation to the surgical procedure as a whole. In 2007, Leslie et al. analyzed the use of the tunica vaginalis as a dorsal graft associated with an onlay island flap of the foreskin in urethral reconstruction surgery in rabbits, through a histopathological analysis. Histological evaluation demonstrated good incorporation of the tissues. The authors concluded

Table 2 - Microscopic findings of four groups in regards to inflammatory cells, fibrosis, epithelium and complications.

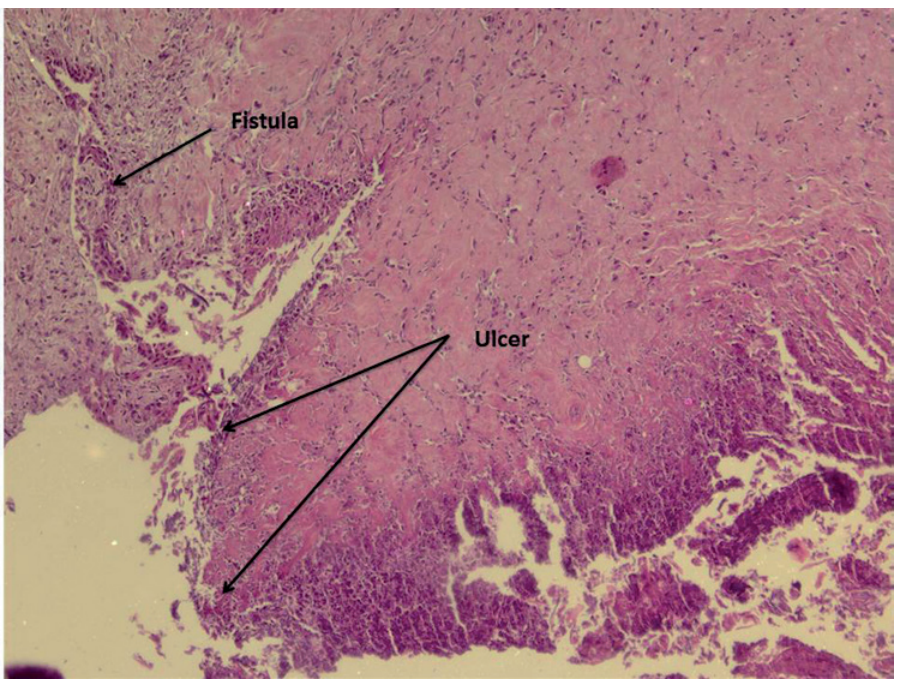
	2 weeks	4 weeks	8 weeks	12 weeks
Polymorphonuclear Infiltrate	2+	1 to 2+	1 to3+	1+
Fibrosis	1 to 2+	1 to 3+	2+	1+
Urethral epithelium	Stratified	Stratified	Stratified	Stratified
	Transition	Transition	Transition	Transition
	Epithelium	Epithelium	Epithelium	Epithelium
Complications	Pyocytes	Pyocytes	Fibrin crust leukocyte	Foreign body reaction
	Foreign body reaction	Granulation tissue	Ulcerations	

that in rabbits, the histological evaluation of a tunica vaginalis graft, applied dorsally over the corpora cavernosa, combined with an onlay flap of the inner foreskin, presented total integration with the adjacent urothelium, good tolerance, and a low level of complications (fistula and diverticulum) (14).

The study by Leslie et al. is similar to ours in its creation of a complex surgical procedure that evaluated a dorsally applied tunica vaginalis graft, as in the analogous three-in-one technique (16). Once again it is worth noticing that even in a complex procedure, also involving a flap and a graft to perform replacement urethroplasty, we observed far fewer complications. In the animals euthanized at 12 weeks (Group 4), there was a reduction in polymorphonuclear cells and an increase in lymphoplasmacytic infiltrate. We also noted that the characteristics of the epithelium of these rabbits were entirely different from the other groups, in which acute inflammation predominated and the squamous epithelium presented ulcerations even to the point of necrosis, probably attributable to the surgical trauma as a whole (Figure-3). In 2001, Hafez et al. compared the application of the tunica vaginalis as a flap versus a graft for the correction of a defect of the tunica albuginea. In this evaluation, the flap showed evidence of an intact blood supply, viability of the cremasteric musculature without necrosis, and collagen remodeling at 12 weeks (11). In contrast, our study did not identify the tunica vaginalis in the histological analysis. We were not able to confirm the presence of the tunica vaginalis mesothelium in our slides. Thus, despite having used a technique similar to theirs, our results regarding the tunica vaginalis did not concur (11). There was no viability of the tunica vaginalis. We suggest that this must be related to the buccal mucosa graft that did not consolidate, leading to intense inflammation and loss of the flap. This study was proposed with the purpose of developing, in an animal model, a surgical technique that enabled a corporoplasty to be performed with a tunica vaginalis flap and urethroplasty with a buccal mucosa graft in a single surgery. However, we are faced with a belief in reconstructive surgery: to apply a graft directly over a flap. We did not find any studies testing this approach, and so we decided to test it.

Previous studies on hypospadias repair in our university presented very good results, with no natural deaths and two cases of fistula in the 16 rabbits in one study (14) and no complications in the other two (15, 17). In contrast, we observed two deaths (at two and eight weeks) and six animals with fistula, four of which presented urinary retention and urethra stenosis. Our complications were, therefore, more frequent and more severe. Our results were very heterogeneous among the rabbits, in terms of both clinical evolution and histological results, which we must interpret carefully. We observed unfavorable clinical outcomes overall, with all animals showing scrotal edema

Figure 3 - Histological representation of epithelial erosion and presence of necrotic tissue in the luminal area of the urethra (group 2 weeks, HE x 40).

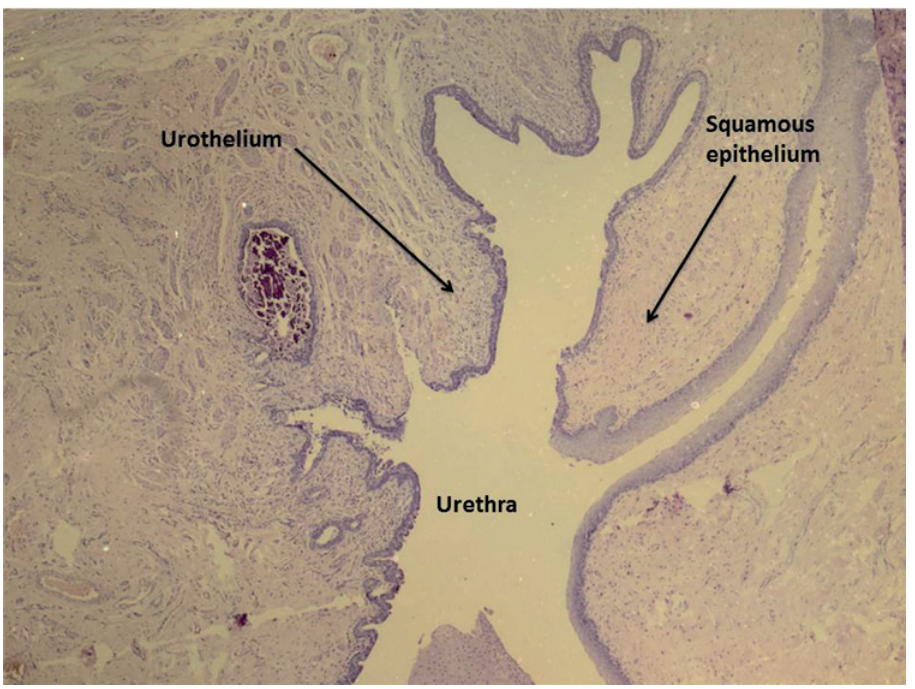


and intense wound hyperemia, progressing to a large number of complications. In the first week, we observed fistula in six animals (75%), three with a high volume of urine release. These data conflict with those from previous studies that involved only one tissue replacement. Histological findings confirm the unfavorable clinical findings, with a pattern of large structural changes, highlighting the absence of epithelialization and tissue regeneration, as well as intense inflammation and architectural lesions, producing fistula (Figure-4), and complicating the repair process. We also observed the formation of abscesses in four animals, with necrosis and a large amount of pyocites, mainly in the urethral lumen. The technique seemed inadequate, considering the high number of complications and unfavorable clinical outcomes. We believe that there is a multifactorial explanation for the failure of the procedure. We understand the complicating factors to be: the complexity of the surgical procedure, the extensive tissue manipulation, with prolonged surgical time, the combined use of dorsal flap and graft, the experimental defect produced in the corpus cavernosum, and the corporoplasty with urethroplasty. Which of these factors contributed to the failure of the procedure failure is something to be investigated in larger samples, with more control groups. Therefore, we recommend performing the surgery for the correction of complex hypospadias in two stages, and discourage the use of graft over flap in clinical series.

CONCLUSIONS

The experimental model of complex hypospadias corrected with dorsal buccal mucosa graft for replacement urethroplasty, ventral flap of foreskin for the ventral region of the penis, and tunica vaginalis flap for corporoplasty; with the tunica vaginalis flap overlaying the onlay buccal mucosa graft for the urethroplasty; and one stage procedure, has resulted in a high number of complications, observed both histologically and in the clinical evolution of the experimental animals. It is not recommended that this procedure for complex hypospadias be reproduced, until the reasons for the failure have been identified.

Figure 4 - Histological aspect of urethral ulceration and fistula formation with marked inflammatory process (group 2 weeks, HE x 40).



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CONFLICT OF INTEREST

None declared.

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Persistent Mullerian Duct Syndrome: a rare entity with a rare presentation in need of multidisciplinary management

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ABSTRACT

Main findings: A typical male looking adolescent with a legal female gender assignment presented with haematuria. Investigations led to the diagnosis of Persistent Mullerian Duct Syndrome. The condition is indeed a rare entity that needs a multidisciplinary team management.
Case hypothesis: A case of Persistent Mullerian Duct Syndrome undiagnosed at birth because karyotyping was defaulted, thus resulting in a significant impact on the legal gender assignment and psychosocial aspects.
Promising future implications: The reporting of this case is important to create awareness due to its rarity coupled with the rare presentation with hematuria as a possible masquerade to menstruation. There were not only medical implications, but also psychosocial and legal connotations requiring a holistic multidisciplinary management.

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INTRODUCTION

Persistent Mullerian Duct Syndrome (PMDS) is a very rare condition with less than 300 cases described in the literature (1, 2). This rare entity showcases adolescents who are phenotypically males with 46,XY karyotypes. However, such individuals harbor internal female reproductive organs which are Mullerian derivatives, rendered by a defect in either genes coding for the Mullerian inhibiting substance (MIS) / anti-Mullerian Hormone (AMH) or the AMH receptor (2), ultimately leading to failure of regression of Mullerian ducts (3).

Scenario

A 14-year-old adolescent with typical male physical appearance, legal gender assigned as female, presented to the emergency department with hematuria. Abdominal ultrasound showed normal sized kidneys with a few small nephrolithiasis of 3-4mm in size. There was no hydronephrosis and the urinary bladder looked normal. However, there was a cystic lesion located postero-superior to the urinary bladder, suspected to be a hydrocolpos. By definition, hydrocolpos refers to the distension of the vagina caused by accumulation of fluid due

to congenital vaginal obstruction. The patient was subsequently referred to the gynecology department for assessment of hydrocolpos.

On further questioning, the patient had intermittent hematuria, however, denied cyclical abdominal pain or backache. The history from the mother revealed a patient who was born prematurely at 32 week's gestation from a non--consanguineous union and who had ambiguous genitalia at birth with the absence of both testes. The patient was referred to a university hospital for further investigation, from which ultrasound of the pelvis detected a uterus-like structure. The baby was given appointment to have karyotyping performed, however the mother had defaulted the investigation as the child's father was terminally ill. With financial restriction, logistic problems, raising the child single-handedly and without any ill intention, the mother had gender assigned this child as a female with the finding of a uterus-like structure.

The child was initially placed in a normal primary school but was unable to follow school routine in view of his mental capacity that is below the average required by normal school; it was advised for her to be admitted to a school for children with special needs. The patient excelled in sports and had the strength of a male–even preferred male peer groups and male attire.

A physical examination revealed an adolescent with a typical male phenotype, height within 50th centile of boys in accordance to race, age and measured height. The patient had facial acne vulgaris, a coarse voice and male pattern hair distribution. Further examination revealed a normal abdomen and inguinal region. An examination of the genitals showed a well-formed penis, with a urethral opening at the ventral aspect of the penile root. There was absence of testes bilaterally in the scrotum; however, no vaginal opening was seen.

Karyotyping showed – 46,XY with SRY gene present. Follicle Stimulating Hormone: 44.09U/L (normal: 0.05-9.60U/L), Luteinizing Hormone: 15.19U/L (0.08-20.62U/L), Total Testosterone: 4.34nmol/L (normal: 10.07-38.76nmol/L), Estradiol: 24.5pmol/L (follicular: 77-921pmol/L, luteal: 77-1145 pmol/L), Aldosterone: 530pmol/L (>11 years old: <582.6pmol/L), Serum Dehydroepiandrosterone: 94ug/dL (20-49 years old, female: 32-380ug/dL, male: 94-640ug/L), Cortisol: 201nmol/L (normal, 9am: 64-536nmol/L), beta HCG: 6.5IU (<5.0IU), alfa fetoprotein 0.9IU/mL (normal: 0-5.8IU/mL), Free Thyroxine: 14.71pmol/L (9.14-23.8pmol/L), Thyroid Stimulating Hormone: 1.66mIU/L (0.27-4.2mIU/L), Insulin-like Growth Factor-1: 403ug/L (normal for 13-15 years old: 142-525ug/L).

MRI of the abdomen and pelvis showed a single cervix, uterus and hydrocolpos (Figures 1 and 2). The uterus had two horns with a flat fundus. There were no definite structures to suggest ovaries. However, there was an oval structure at the left hemi pelvis, medial to the external iliac vessels, suggestive of a testis, measuring 1.2x1.2x2.3cc. A cysto-genitoscopy noted an opening at the posterior and distal

Figure 1 - MRI of the pelvis and abdomen of the patient, showing the bladder (B), a single cervix and uterus (U), and two tubular structures at the usual place of corpus cavernosum (P). Structures suggesting the ovaries are not seen. The uterus has two horns, however it has flat fundus which is in favor of incomplete septate uterus. An oval intermediate signal intensity at left hemipelvis, medial to external iliac vessels, is suggestive of a testes. It measured 1.2cm x 1.2cm x 2.3cm.

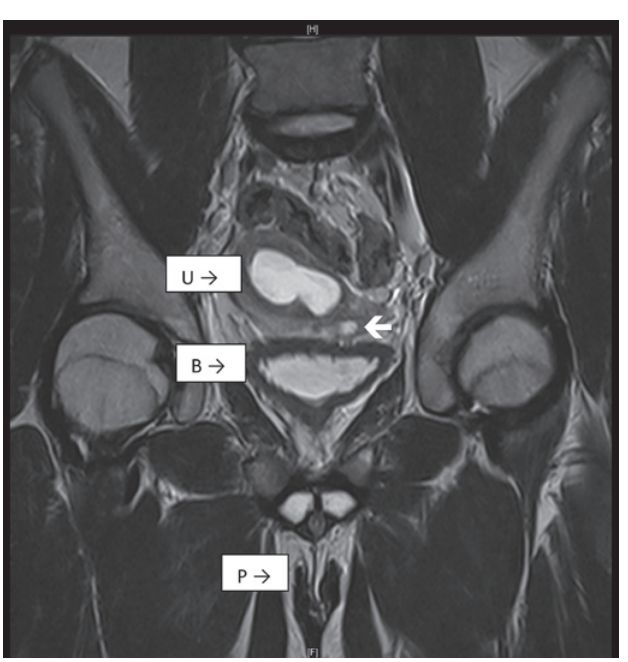
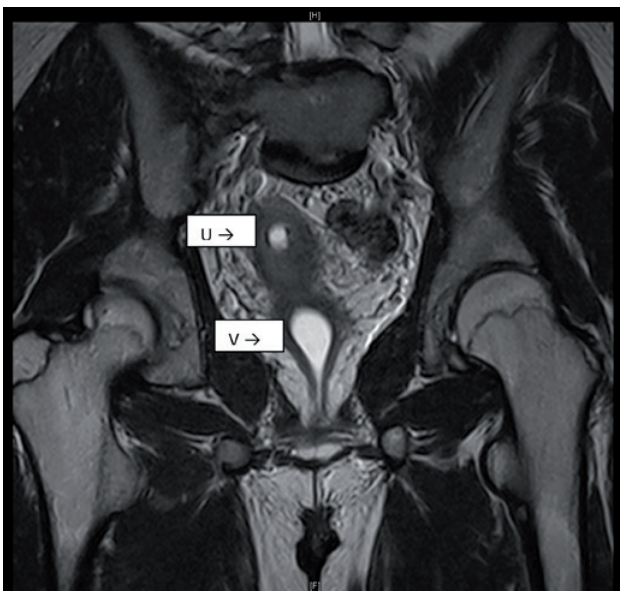


Figure 2 - MRI of the pelvis, showing the uterus (U) and the hydrocolpos (V).



part of the bladder neck, enabling the scope to pass through, finding blood clots in a space possibly representing the vagina. A cervix was not identified. The urethra, bladder and urethral opening were otherwise normal.

Diagnostic abdominal laparoscopy revealed a tubular structure in the left pelvic region, which might represent a streak gonad, with another tubular structure situated superiorly, a possible Wolffian remnant. A bicornuate uterus with a more prominent right horn was identified with a long tubular structure connected to the right uterine horn that represented a fallopian tube. No gonad was identified at the distal end of the fallopian tube. A rounded structure enlarged to the superior of the uterus was characterized as a possible hydrocolpos.

A diagnosis of PMDS with one identified abdominal testis was made. Subsequently, the child and the mother requested for a legal change in gender assignment due to the problems faced. The patient was referred to joined management with a urologist, a pediatric surgeon and a pediatric adolescent psychiatrist. An application for legal gender change was filed and the child was subsequently planned for hysterectomy with the excision of the hydrocolpos and the streak gonad.

DISCUSSION

The mechanism of PMDS is likely to be multi-factorial, although there have been reports of consanguinity. An autosomal recessive inheritance seems to affect the majority (85%) of cases (2); however, the origin of the remaining 15% of cases remains unknown (3). Nonetheless, the case reported did not arrive from a consanguineous union (2).

The condition exhibits a wide variation in the age of presentation, being reported in a man with 77 years of age (1). It may also be undiagnosed, as in some cases the Mullerian derivatives do not give rise to any problems to the bearer. A list of the PMDS cases reported in the literature in the last five years is provided in Table-1 (4-26). And up to date, there are no reported cases of association with mental abnormality with PMDS. Therefore, we believe that the patient has coincidental mental handicap.

This child had previously presented with hematuria, without which he might have remained silent in his anguished female-assigned role. Ultrasound of kidney, ureter and urinary bladder was performed, from which hydrocolpos was detected. Hematuria, here, could be renal of origin or a mixture of urine with menstrual blood from a possible functioning uterus. This patient, however, did not have other associated symptoms of colicky pain or dysuria to suggest renal origin. In a study involving 292 children, about 15% of the subjects with renal calyceal microlithiasis of <3mm presented with hematuria, suggesting the minute size of calculi and their ability to pass through the urinary tract do not aggravate crystaluria (27). A previous review on nephrolithiasis in children revealed that about 30% of children present with gross hematuria; however, only 4 out of 50 children with the presence of an average of 2.3mm urolithiasis have clinical symptoms leading to diagnosis of distal ureteral stones (28).

The serum hormonal profile showed a corresponding picture of testicular failure in which he had a high FSH level and a low testosterone level from the hypo-production of the streak male gonad. In the management of young children with undescended testes, serum AMH measurement can be beneficial

Table 1 - Case reports of Persistent Mullerian Duct Syndrome (PMDS) in the last five years*

First author and year (ref. number)	Country	Patient characteristics
Tosur 2015 (4)	United States	A genetic male with PMDS and AMH deficiency associated with distal monosomy 10q.
Modi 2015 (5)	India	An adult male with bilateral cryptorchidism and a pelvic mass, who presented with acute urinary retention, and was diagnosed with a seminoma of the right testis, intratubular germ cell neoplasia of the left testis with the presence of Mullerian remnants.
Yamada 2015 (6)	Japan	A 42-year-old man with testicular seminoma and transverse testicular ectopia.
Kovachev 2014 (7)	Bulgaria	A 46-year-old man with a history of cryptorchidism and orchidopexy and father of two children presenting with an intra-abdominal mass.
Telli 2014 (8)	Turkey	A patient with testicular ectopia.
Morikawa 2014 (9)	Japan	A 1-year-old child presented with bilateral cryptorchidism and normal male external genitalia. A laparoscopic surgery revealed a uterus and fallopian tubes.
Wei 2014 (10)	Taiwan	Three patients with bilateral undescended testis and Mullerian duct remants.
Alp 2014 (11)	Turkey	A 28-year-old male diagnosed with undescended left testis and infertility (azoospermia).
Wu 2014 (12)	United States	An infant born with hypospadias and no palpable gonads was diagnosed with PMDS based on history, physical examination, laboratory testing, and radiologic imaging. A robot-assisted laparoscopic hysterectomy, right gonadal biopsy, and bilateral orchidopexy were performed.
Farag 2013 (13)	United Kingdom	A young male with a left sided inguinal hernia in which the sac contained both testes and uterus.
Beatty 2013 (14)	United States	A 50-year-old man with a history of hernia repair and vanished testes presenting with abdominal pain, who was diagnosed with an abdominal mass shown to be an uterus and ovary.
Gupta 2013 (15)	India	A 23-year-old man presented with a left-sided reducible inguinal hernia and undescended testis in an empty ill-developed right hemiscrotum. Semen analysis revealed azoospermia and laparoscopy demonstrated a uterus, fallopian tube and a testis.
Wongprasert 2013 (16)	United States	A 2-week-old newborn presented with bilateral cryptorchidism and normal male external genitalia. At age 1 year and 4 months, he underwent laparoscopic surgery, which revealed a uterus and fallopian tubes. A unique homozygous T to G base substitution was found at position 2219, near the middle of the exon 5, changing codon CTG to CGG in anti-Mullerian hormone (AMH) gene. Both parents are heterozygous for the mutation.
Østergren 2013 (17)	Denmark	One patient with unilateral undescended testes and PMSD found during laparoscopy.
Ju 2013 (18)	China	Three cases of Chinese patients with PMDS associated with testicular ectopia, which were subjected to orchidopexy.
Salehi 2012 (19)	United States	Description of 8 cases diagnosed in California.
Keukens 2012 (20)	Netherlands	A 12-year-old boy with cryptorchidism and PMSD diagnosed during laparoscopy.
van der Zwan 2012 (21)	Netherlands	A PMSD patient diagnosed with a novel homozygous missense mutation in the AMH gene (single nucleotide insertion (C) at position 208 Biopsy of both gonads revealed that germ cells were present in an irregular distribution, but the absence of OCT3/4, PLAP and c-KIT expression indicated physiological maturation.
Bassani 2012 (22)	Italy	A patient with PMDS and ITGCNU.
Farikullah 2012 (23)	United Kingdom	Eleven cases with PMDS and malignancy of the Müllerian remnants were reported: five males presented with bilateral undescended testes and three had unilateral undescended testis.
Chattopadhyay 2011 (24)	India	A phenotypically normal looking male presenting with irreducible left sided inguinal hernia, which on exploration revealed uterus, fallopian tubes and testis.
Demir 2011 (25)	Turkey	A 37-year-old man with history bilateral cryptorchidism, erectile dysfunction and infertility; diagnostic laparoscopy confirmed the presence of intra-abdominal testes and PMDS.
Kaul 2011 (26)	United States	An adult male who had a unique combination of both transverse testicular ectopia and PMDS presenting as an incarcerated inguinal hernia.

* Pubmed; articles in English. **AMH** = anti-Mullerian hormone; **ITGCNU** = intratubular germ-cell neoplasia of unclassified type.

in assessing the gonadal function, reflecting the normal development of male genitals. A measurable AMH in a boy who presented with bilateral cryptorchidism is predictive of undescended testes, while undetected AMH is suggestive of anorchia or the presence of ovaries as in cases of pure gonadal dysgenesis or female pseudohermaphroditism (29, 30). Unfortunately, AMH was not measured due to unbearable cost to the family.

The testicular descent indeed is a very complex process influenced by different hormones. Insulin-like hormone 3 (INSL3) is a Leydig cell hormone, which controls the initial gubernacular enlargement (31). Androgens control the inguino-scrotal migration, possibly following signaling from the mammary line and the genito-femoral nerve (31). Although the abnormal long gubernacular cord in cases of PMDS remains unexplained, it is possible that this feature relates to lack of decrease in gubernaculum size that coincides with the complete descent of the testicle-a phenomenon that is androgen-dependent (32). It has been shown that androgen deficiency is associated with failed regression of the gubernaculum and cryptorchidism (33). Despite recent discoveries concerning testicular migration, there are more complex processes that need further understanding. To some, orchidopexy is recommended in the first year of life in view of increasing reports on the formation of stem cells for spermatogenesis to occur between 3 and 9 months of life. Although the aim of surgery is to restore this process and prevent abnormal gonocyte maturation, this is yet to be further confirmed. On the other hand, there is the acquired type of undescended testis, usually presenting later in childhood (34). It occurs when the spermatic cord elongation fails between birth and puberty, so that the initially descended testis is left behind as the scrotum moves further from the groin as the boy enlarges. The prognosis for this variant seems to be better than congenital undescended testis because gonocyte development in the first year should be normal while the testis is still in the scrotum. Currently, orchidopexy and hormonal treatment are valid treatment options for acquired undescended testis; however, many prefer the scrotal surgery when the testis is not residing spontaneously in the scrotum (31).

Patients with PMDS and gonadal dysgenesis who have Y chromosome material are at increased risk for developing germ cell tumors such as gonadoblastoma or carcinoma in situ, with the potential for malignant transformation to dysgerminoma or seminoma, respectively. The prevalence of germ cell tumors in such patients varies from 15-40% (35). The evidence for routine screening with serum tumor markers is equivocal, albeit mandatory if the patient has a gonadal mass on pre-operative imaging (36). If tumor markers are positive, a staged surgical procedure (laparotomy instead of laparoscopy) is indicated. In patients with streak intra-abdominal gonads, gonadal biopsy has no role, as these patients ultimately require gonadectomy to prevent development of a malignancy (36). Recent literature advocates simultaneous hysterectomy and orchidopexy (2), with the laparoscopic approach gaining popularity in recent years (37, 38). The question of reversion of virilization after gonadectomy was not an option for our patient; hence, life-long testosterone replacement therapy was advised.

The request for legal change of gender assignment is valid; however, it might have been avoided if karyotyping had been performed earlier at birth, with the discovery of ambiguous genitalia with bilateral undescended testes. Given the circumstances that surrounded the family's condition at that particular moment, that is the serious illness of one parent, financial restrictions and logistic problems rendered the default to treatment. The failure to understand the seriousness of the problem and its future implications presumably has led to the patient's mistaken identity. Therefore, it was crucial to involve a pediatric/adolescent psychiatrist for the evaluation of the psychological impact of being raised as a female and whether a gender re-assignment would have any significant negative impact on the patient.

Gender assignment is a controversial issue in cases of disorders of sexual differentiation (DSD). Based on no documented report of

malignant transformation in fully descended testes, some advocate male gender assignment to significantly virilized patients with completely bilateral descended testes. Another school of experts prefers female gender assignment in patients who have a uterus and a vagina and who are under-virilized and are markedly short in height (39). In our case, however, it was interesting to find a completely virilized adolescent with low testosterone. Nevertheless, a possible explanation for this finding is that such patients grow up with lower than normal levels of testosterone and hence their threshold of normal testosterone required for virilization is lower, as seen in other genetic conditions in which virilization is achieved despite having low testosterone levels (e.g. Klinefelter syndrome and 46,XX DSD).

Importantly, there were many issues that needed to be addressed in this patient; hence, several experts from various fields, including urologists, gynecologists, geneticists and psychiatrists, were organized to evaluate the patient. Thus, a comprehensive multidisciplinary team management is the recommended method of managing similar cases with rare disorders of sexual differentiation of complicated nature in the future 5-6, (40).

CONCLUSIONS

A clinically challenging case of Persistent Mullerian Duct Syndrome is discussed that required a multidisciplinary team approach, delineating each and every problem with the aim to create awareness among health care providers of a rare entity.

CONFLICT OF INTEREST

None declared.

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Pure Yolk sac presenting with inferior vena cava thrombus extending from bilateral external iliac veins to hepatic vein

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ABSTRACT

Introduction: Vena cava thrombus is an extremely rare complication of testicular tumors. We report on an unusual case of testicular tumor presenting with inferior vena cava thrombus extending from the left spermatic and bilateral external iliac veins to the hepatic vein.
Case report: A-35-year old man presented with a 6-month history of left scrotal mass and a 1-day history of bilateral lower extremity edema. Computed tomography (CT) revealed the presence of thrombus extending from the left spermatic vein and bilateral external iliac veins to the hepatic vein, and multiple lymph node and lung metastases. 3 cycles of chemotherapy were given after the left high inguinal orchiectomy. Pathological examination demonstrated a pure yolk sac carcinoma with lymphovascular invasion and direct tumor extension into the left spermatic cord. CT and positron emission tompgraphy-CT obtained no findings of metastasis or recurrence at 3 months after the chemotherapy.
Conclusion: We review this seldom case and discuss the literature with regard to its diagnosis and treatment.

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Keywords:
Yolk Sac; Testicular Neoplasms; Vena Cava, Inferior; Thrombosis

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INTRODUCTION

Inferior vena cava thrombus due to a testicular tumor is an extremely rare condition. There have been a few reports of thrombus due to testicular tumor extended to inferior vena cava in literature. Most of pathological examinations revealed mixed germ cell carcinoma which generally consisted of embryonic carcinoma (1-3). We presented a case of pure yolk sac testicular tumor with the thrombus of inferior vena cava extended from the left spermatic and bilateral external iliac veins to the hepatic vein.

CASE REPORT

A 35-year-old man was admitted to the hospital complaining of bilateral lower extremity edema. He reported a six-month history of painless mass in the left scrotum. Physical examination disclosed a 10 x 6cm firm non-tender left scrotal mass. A thorax computed tomography (CT) demonstrated multiple metastases in both lungs. Abdomen enhanced CT revealed retroperitoneal multiple lymph node metastases, inferior vena cava thrombus extended from the left spermatic vein and bilateral external iliac veins to

the hepatic vein and a decrease in the function of the left kidney due to a thrombus of the left renal vein (Figure-1). Color Doppler ultrasound confirmed complete occlusion of the inferior vena cava, the left renal and bilateral common iliac veins. Serum tumor markers were high except beta human chorionic gonadotropin (ß-HCG): lactate dehydrogenase (LDH), 441U/L (120-246); alpha-fetoprotein (AFP), >1000ng/mL (<8); ß--HCG, 0.2mIU/mL (<1.0).

A left high inguinal orchiectomy was performed and pathological diagnosis was pure yolk sac carcinoma with lymphovascular invasion and direct tumor extension into the left spermatic cord. Three cycles of bleomycin, etoposide, and cisplatin (BEP) were given. A nearly complete response in the retroperitoneal and lung metastases was observed by thorax and abdominal CT (Figure-2), tumor markers were normalized at 3 months after this chemotherapy. Although the patient did not have any several respiratory complaints, thorax CT showed partial embolism in the right pulmonary artery and bronchial mass. Anticoagulant treatment was begun and then bronchoscopy with biopsy was performed. Pathological and microbiological examination revealed mycobacterium tuberculosis. Anti-tuberculosis therapy was started and an inferior vena cava filter was implanted through the right internal jugular vein. The inferior vena cava remained occluded, with evidence of collateralization such as the improvement of the left renal function. CT and positron emission tomography (PET-CT) showed no findings of metastasis or local recurrence at 6 months after the surgery.

DISCUSSION

Thrombus of inferior vena cava due to testis tumor is an extremely seldom condition. In earlier cases (1-7), most of pathological examinations revealed embryonic carcinoma or mixed non-seminomatous germ cell carcinoma that usually consisted of embryonic carcinoma. Kinebuchi et al. reported that the embryonic carcinoma component in the primary testicular tumor with inferior vena cava thrombosis was relatively high (7). This high rate may be due to the aggressive behavior of embryonic carcinoma. The presented case was the first patient who had inferior vena cava thrombus due to pure yolk sac testis tumor according to our knowledge of the literature. Although yolk sac is a less aggressive tumor than embryonic carcinoma, it caused the inferior vena

Figure 1 - Computerized tomography scan of the abdomen demonstrating the inferior vena cava thrombus extended from the left spermatic vein and bilateral external iliac veins to the hepatic vein, retroperitoneal multiple metastasis and the impairment of the left renal function.

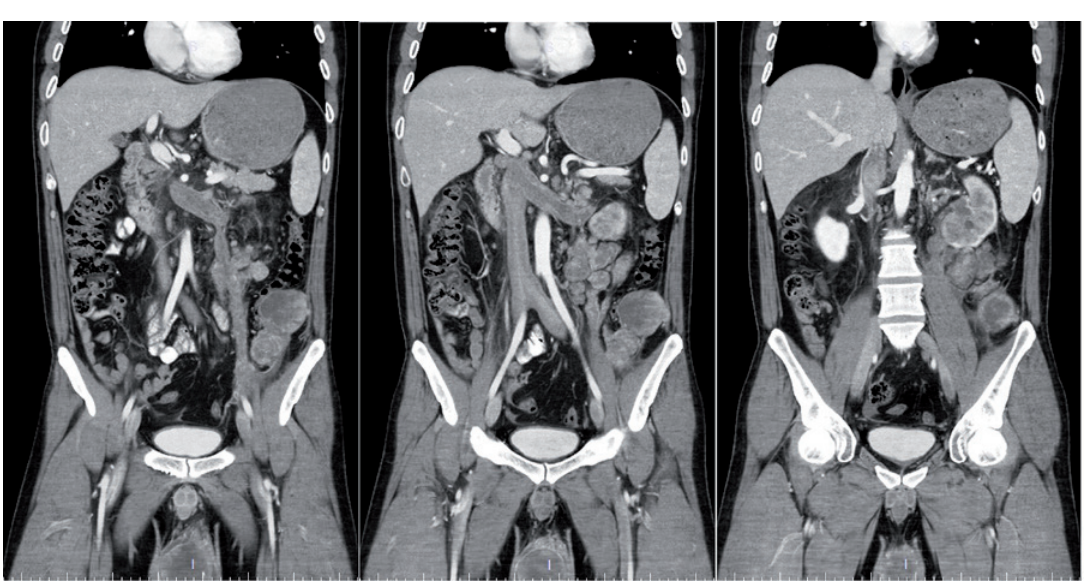
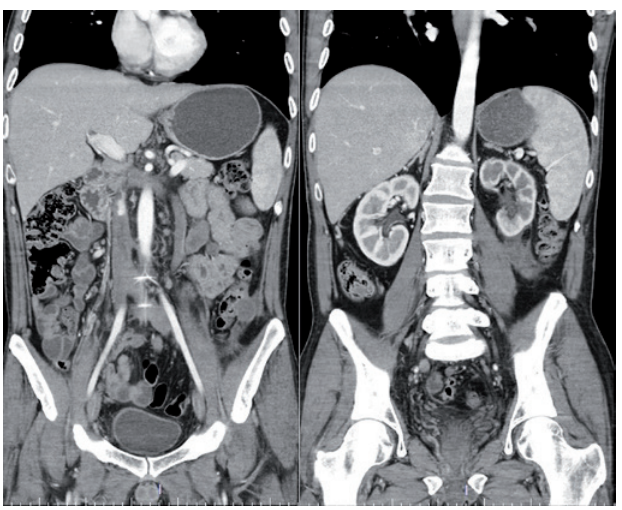


Figure 2 - Computerized tomography scan of the abdomen demonstrating the inferior vena cava thrombus extended from the left spermatic vein and bilateral external iliac veins to the hepatic vein, no evidence of metastasis, and the improvement of the left renal function at 3 months after the treatment.



cava thrombosis of the present case. This may be due to the long term history (six months) of painless testicular mass in the patient.

Since the inferior vena cava thrombus lengths of earlier cases had been generally short, these patients were treated with either chemotherapy alone or surgery excision of thrombus after the chemotherapy (4-7). Only one case was reported with inferior vena cava thrombus extended from the infrarenal level to the common iliac veins (8). This patient underwent high inguinal orchiectomy and chemotherapy. Since the radiological imaging showed no evidence of metastasis at 4 months the treatment, additional therapy was not performed for this case. Surgery excision was not performed for the occluded inferior vena cava because of collateralization.

Our case had inferior vena cava thrombus extended from the left spermatic vein and bilateral external iliac veins to the hepatic vein. The radiological imaging (CT and PET-CT) indicated no evidence of metastasis or recurrence after orchiectomy and chemotherapy. Although the inferior vena cava remained occluded completely, there were evidences of collateralization such as the improvement of the left renal function and disappearance of lower extremity edema. Overall, we discussed with the present patient and decided not to performed surgery excision of inferior vena cava thrombus.

Testicular tumor presenting with thrombosis of the inferior vena cava, with or without subsequent pulmonary embolism, can be managed with a combination of anticoagulation and/or inferior vena cava filter placement. The present patient was begun anticoagulation therapy before the chemotherapy for the risk of pulmonary embolism but a filter was not placed into the inferior vena cava. After partial pulmonary embolism occurred, the filter was placed into inferior vena cava. We suggest that a filter should be placed and started anticoagulation therapy before the chemotherapy because of the risk of pulmonary embolism.

CONFLICT OF INTEREST

None declared.

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VIDEO SECTION

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Retroperitoneoscopic pyelolithotomy: a good alternative treatment for renal pelvic calculi in children

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ABSTRACT

Introduction: Nephrolitiasis, once considered an adult disease, has become increasingly prevalent in children, with an increase from 6% to 10 % annually in past 25 years. Kidney stones in pediatric population can result from metabolic diseases in up to 50% of children affected. Other factors associated with litiasis are infection, dietary factors, and anatomic malformations of urinary tract.

Standard treatment procedures for pediatric population are similar to adult population. Extracorporeal shock wave lithotripsy (ESWL), ureterorenoscopy (URS), percutaneous nepfrolithotomy (PCNL), as well as laparoscopic and retroperitoneoscopic approaches can be indicated in selected cases.

The advantages of laparoscopic or retroperitoneoscopic approaches are shorter mean operation time, no trauma of renal parenchyma, lower bleeding risk, and higher stone-free rates, especially in pelvic calculi with extrarenal pelvis, where the stone is removed intact.

Patient and Methods: A 10 year-old girl presented with right abdominal flank pain, macroscopic hematuria,with previous history of urinary infections.. Further investigation showed an 1,5 centimeter calculi in right kidney pelvis. A previous ureterorenoscopy was tried with no success, and a double J catheter was placed.

After discussing options, a retroperitoneoscopic pielolithotomy was performed.

Results: The procedure occurred with no complications, and the calculi was completely removed. The foley catheter was removed in first postoperative day and she was discharged 2 days after surgery. Double J stent was removed after 2 weeks.

Conclusions: Retroperitoneoscopic pielolithotomy is a feasible and safe procedure in children, with same outcomes of the procedure for adult population.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMENT: RETROPERITONEOSCOPIC PYELOLITHOTOMY: A GOOD ALTERNATIVE TREATMENT FOR RENAL PELVIC CALCULI IN CHILDREN

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This video Cezarino et al. (1) was very well about a retroperitoneal laparoscopic pyelolithotomy. While executed flawlessly, the applicability of this video to the average urologic practice is limited because of the other treatments readily available that are usually exhausted prior to laparoscopic stone surgery. Generally, open and robotic/laparoscopic approaches are used in combination with procedures for coexisting anatomic abnormalities. PCNL, ESWL, and ureteroscopy are safe, available at most institutions and should be utilized in the pediatric population as first-line therapy (2). Despite this, the video does add to the literature and will be needed as a guide for those rare cases when laparoscopic stone surgery is needed.

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VIDEO SECTION

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Retzus-sparing robotic-assisted laparoscopic radical prostatectomy: a step-by-step technique description of this first brazilian experience

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ABSTRACT

Introduction: Retzus-sparing robotic-assisted radical prostatectomy(RARP) is a newly approach that preserve the Retzus structures and provide better recovery of continence and erectile function. In Brazil, this approach has not yet been previously reported.
Objective: Our goal is to describe Step-by-Step the Retzus-sparing RARP surgical technique and report our first Brazilian experience.
Methods: We present a case of a 60-year-old white man with low risk prostate cancer. Surgical materials were four arms Da Vinci robotic platform system, six transperitoneal portals, two prolene wires and Polymer Clips. This surgical technique was step-by-step described according to Galfano et al. One additional step was added as a modification of Galfano et al. Primary technique description: The closure of the Denovellier fascia.
Results: We have operated one patient with this technique. The operative time was 180minutes, console time was135 min, the blood loss was 150ml, none perioperative or postoperative complications was found, hospital stay of 01 day. The anatomopathological classification revealed a pT2aN0M0 specimen with free surgical margins. The patient achieved continence immediately after bladder stent retrieval. Full erection reported after 30 days of surgery.
Conclusion: Retzus-sparing RARP approach is feasible and reproducible. However, further comparative studies are necessary to demonstrate potential benefits in continence and sexual outcomes over the standard approaches.

CONFLICT OF INTEREST

None declared.

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LETTER TO THE EDITOR

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RE: White blood cell counts and neutrophil to lymphocyte ratio in the diagnosis of testicular cancer: a simple secondary serum tumor marker

Ozgur Haki Yuksel [1], Ayhan Verit [1], Aytac Sahin [1], Ahmet Urkmez [1], Fatih Uruc [1]
Int Braz J Urol. 2016;42:53-9.

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To the editor,

We read the article by Yuksel et al. (1) entitled "White blood cell counts and neutrophil to lymphocyte ratio in the diagnosis of testicular cancer: a simple secondary serum tumor marker" published in your journal. This is a very interesting study which is very well-designed and presented. Yuksel and coworkers has evaluated the white blood cell (WBC) counts and neutrophil to lymphocyte ratio (NLR) as markers of systemic inflammation in the diagnosis of localized testicular cancer as a malignancy with initially low volume. They have shown that (WBC) counts and NLR were statistically significantly higher in patients with testicular cancer compared with the control group. They have defended that both (WBC) counts and NLR can be used as a simple test in the diagnosis of testicular cancer. We respectfully thank the authors for this contribution.

Testicular cancer is the most common cancer in young men. Commonly, most testicular cancers indicate with palpable mass and are malignant in 90-95% of all cases. Standard treatment for testicular cancer is radical orchiectomy (2-4). Preoperative exhaustive evaluation with physical examination, tumour markers, and ultrasonography, can lead to better diagnosis of testicular cancer. AFP, HCG and LDH were defined as tumor markers in testicular cancer (5). Serum tumour markers are prognostic factors and conduce to diagnosis and staging. Serum tumour markers should be detected before, and 5-7 days after, orchiectomy (5). Tumour markers are of value for diagnosis (before orchiectomy) as well as for prognosis (after orchiectomy).

Routine peripheral blood counts may be beneficial in prognosis and diagnosis of many disorders, involving testicular cancer (1, 6-13). NLR is measured by dividing the number of neutrophils by the number of lymphocytes. NLR is used as an inflammatory marker in the inflammatory disorders. Inflammation has an crucial role in the proliferation, angiogenesis, and metastasis of cancer cells and is substantial in the development and progression of the disease (14, 15).

NLR is easily measurable laboratory marker used to appraise systemic inflammation. These marker maybe related with many circumstances such as thyroid function abnormalities, renal and/or hepatic dysfunction, diabetes mellitus, hypertension, chronic obstructive respiratory disease, meta-

bolic syndrome, malignancy, B12 and folic acid deficiency, inflammatory diseases, local and/or systemic infection, smoking, alcohol consumption, anemia, and any use of medication (immunosuppressive agents corticosteroids and non-steroid anti-inflammatory drugs) related to inflammatory status of patients (6-13). In this study only excluded who patients with an evidence of concomitant infection or inflammation. The authors should have mentioned these factors.

In conclusion, we strongly believe the findings obtained from the current study will lead to further studies examining the WBC counts and NLR in the diagnosis of testicular cancer.

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LETTER TO THE EDITOR

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RE: Dipstick Spot urine pH does not accurately represent 24 hour urine PH measured by an electrode

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Int Braz J Urol. 2016;42:546-9.

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To the editor,

Dear Editor, the recent report on "Dipstick Spot urine pH does not accurately represent 24-hour urine pH measured by an electrode" is very interesting (1). Similar to the previous report by Kwong et al., the diagnostic property of urine dipstick is the issue for consideration. In fact, it is no doubt that the urine dip stick cannot be comparative to automated electrode urine chemistry analyzer. However, the usefulness of dipstick is still noted and should be mentioned. First, the use of dipstick is fit for field work where the advanced technology is not available. To help the accuracy, the use of semi-automated urine strip reader might be a solution for the problem of naked eye urine strip reading. Nevertheless, it should be noted that the urine dip stick can be only a screening tool. The confirmation is noted. As noted by Wockenfus et al. "therapy protocols should not alternate between dipstick and pH meter urine pH monitoring (3)."

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