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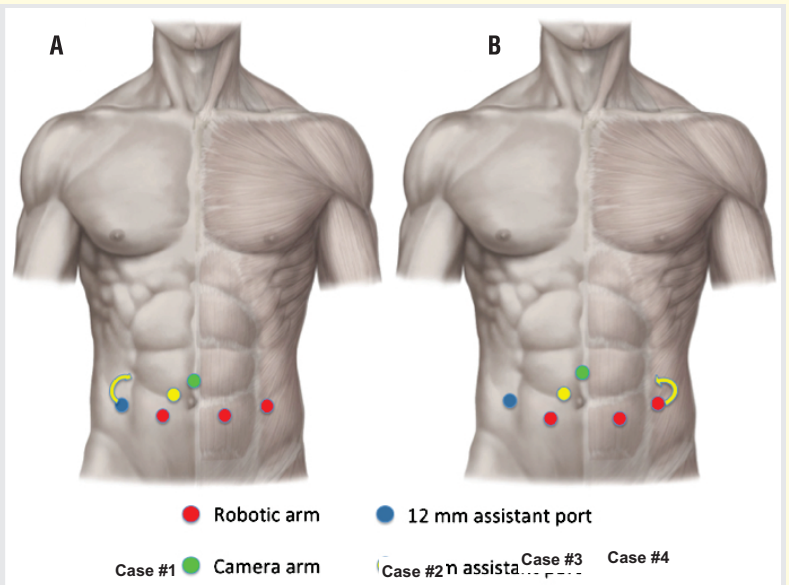

Figure 1 - Robotic and assistant port positioning for T-RARP.

A) The placement of the 12 mm assistant port was modified, medially and cranially respect to the standard set, in case of right kidney graft location. B) The placement of the third robotic arm was modified, medially and cranially respect to the standard set, in case of right kidney graft location. (*Page 264*)

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VIDEO SECTION

LETTER TO THE EDITOR

EDITORIAL
IN THIS ISSUE

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The future of inguinal Lymphadenecotmy in penile cancer: laparoscopic or robotic?

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The March-April 2019 issue of the International Braz J Urol presents original contributions with a lot of interesting papers in different fields: Prostate Cancer, Renal stones, Renal Cell Carcinoma, Bladder Cancer, Uretrhal Strictures, Trauma, Prostate Biopsy, Kidney Transplant, neurogenic Bladder and Penile Cancer. The papers come from many different countries such as Brazil, USA, Turkey, China, Italy, Iran, Argentina, Spain, South Korea, and United Kingdon, and as usual the editor's comment highlights some papers. We decided to comment the paper about a very interesting topic: The treatment of the inguinal lymph nodes in penile cancer.

Doctor Meneses and collegues from Brazil performed on page 325 an interesting study about the Video Endoscopic management of inguinal lympadenectomy in penile cancer. The authors described the initial experience with this method and analyzed the post-surgical complications in 11 patients with penile cancer (stages T2 or T3). They observed the bleeding, drainage time, cellulitis, lymphocele, cutaneous necrosis, miocutaneous necrosis and hospitalization time. The results of the paper shows that no patient showed intrasurgical complications, bleeding > 50 mL or conversion. The global complication rate was 33.2% (27.2% were lymphatic). No patient showed cutaneous necrosis. The authors concluded that video endoscopic management of inguinal lympadenectomy in penile cancer is a safe and easy technique with lower incidence of complications.

Malignant neoplasm of the penis is a rare disease, being more common in regions with low socioeconomic levels, accounting for approximately 2% of malignancies in man, with squamous cell carcinoma (SCC) being the most common type (1, 2). Considering that tumor dissemination is preferentially done lymphatic (initially for superficial inguinal lymph nodes and later for deep inguinal and pelvic lymph nodes), the presence of metastases in the inguinal lymph nodes is the main variable capable of affecting the survival in these patients (3). In this way, bilateral inguinal lymphadenectomy represents the only procedure capable of identifying and treating inguinal micrometastases early, although its prophylactic indication is controversial in the literature (4-6). The following are the main indications of lymphadenectomy: tumors > 2 cm, high-grade tumors (histopathological grade II or III), advanced local staging (T2-T4), lymphovascular microscopic invasion, palpable inguinal lymph nodes after antibiotic therapy, palpable inguinal lymph nodes that appeared in the follow-up without evidence of distant disease and unsatisfactory clinical evaluation (obese, inguinal surgery) (4).

Inguinal lymphadenectomy represents an important stage of treatment. However, it should be noted that about 50% of patients submitted to open

inguinal lymphadenectomy have important complications, such as wound infection (26%), necrosis and dehiscence of operative wound (41%) and lymphocele (21%) thus being a procedure with high morbidity (5, 6). The paper of Meneses and collegues shows that laparoscopic video technique is a very good option, but the authors had 30% of complications. In a recent paper where the outcomes between open and robotic surgery were compared a multivariable analysis shows that the pathological nodal stage and open inguinal lymph node dissection were the independent risk factors associated with an increased risk of major complications (7). A systematic review published in the present year shows lower rates of complications of robotic surgery compared with open surgery (8).

We need more evidences, but we can conclude that robotic surgery will be the gold standard treatment for inguinal lymphadenectomy in penile cancer.

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DIFFERENCE OF OPINION

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Super active surveillance for low-risk prostate cancer | *Opinion: Yes*

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Keywords: Prostatic Neoplasms; Risk Reduction Behavior; Watchful Waiting; Therapeutics

Prostate cancer is the most common solid tumor in men in western countries. Notwithstanding, its high incidence, most patients survive their prostate cancer diagnosis and die from other causes (1). This low cancer death event rate poses remarkable challenges for both patients and their treating physicians. Fundamentally the "overs", meaning overdiagnosis and overtreatment (2). Both particularly important as significant issues for patients arise as consequences of treatment. Distastefully, urinary incontinence and erectile dysfunction, among other, both exerting substantial impact in quality of life (3).

This decade has witnessed results from three randomized trials. These robust studies clearly pointed to a limited benefit of definitive intervention such as surgery or radiation vs. surveillance modalities. The lack of differences in all cause survival and the relative low rate of metastasis 10 and 15 years after diagnosis have changed dramatically our knowledge on what is best to do when a man presents with a newly diagnosed prostate cancer (4-6).

Not surprisingly, active surveillance (AS) has become a definitive alternative and common option. This strategy of management certainly decreased the morbidity rates associated to radical surgery or radiation (7). Specifically, AS is now a preferred option for many men with low-risk prostate cancer, gaining worldwide adoption due to robust data and is currently highlighted by many guidelines as the best treatment strategy for men with low risk (8, 9).

What constitutes the best approach to AS is an open question, as many protocols currently exists. However, to the patient selection questions, the field of urology sets the tone in low risk - PSA <10 ng/ml, WHO GG1 and a clinical stage T1c/T2a. There are several stricter protocols that have been developed and tested for AS. The Epstein criteria of ≤2 positive cores, <50% core involvement, and PSA density <0.15 ng/ml/cm^3 carries 10 years rates of overall survival, cancer-specific survival, and metastasis-free survival of 94%, 99.9%, and 99.4%, respectively. Importantly, at 15 years, oncological outcomes such as metastasis-free survival and cancer specific survival change little (10).

In Canada, specifically Klotz and collaborators have reported on single-arm cohorts of low--risk patients (Gleason score ≤6 and serum PSA level ≤10 ng/mL) and favorable intermediate-risk patients (serum PSA ≤15 ng/mL or a Gleason score of 7 [3+4]). The investigators reported 10- and 15-year metastasis-free survival rates of 96% and 95% vs 91% and 82% for low vs. intermediate

risk patients, respectively. Clearly the results are more consistent with low risk patients (11).

Nevertheless, a low-risk categorization does not equal to an indolent course. The presence of Gleason pattern 4 or 5 in patients diagnosed as low risk is about 30%, not insignificant (1). Importantly, as shown recently by Diamand et al., the upgrading phenomenon is persisting even as we trend into MR fusion biopsies. These researchers evaluated the accuracy in histologic grading of final histopathologic outcomes of radical prostatectomy specimens compared to systematic biopsies (SB), targeted biopsies (TB) and the combination of both (SB+TB). There was an upgrade by the final prostatectomy specimens of 43.1%, 39.5% and 23.9%, respectively (12).

Thus, the debate of AS is anything more intense and relevant than ever. As we described before, AS is particularly susceptible to perceptions and bias, life intricacies of both patients and their treating physicians (13). Compliance in AS demands a commitment, significant intellectualization, and conviction to ameliorate the anxiety motivated by thoughts, either own or from else, that the diagnosed cancer may mutate and go wild. In addition, the 2-year reclassification rates of patient in AS ranges from 49-64% (14). Thus, not uncommonly, many physicians have a low fuse for AS failure and recommend radical interventions. Not surprising, by 5 to 10 years after initiating AS more than 60% of patients change to radical management (15-19).

Perhaps the most critical caveat for AS and prostate cancer management in general is the black and white fixed view. We either treat the entire gland or we do not treat at all. This type of dilemma is pervasive to prostate cancer. In our urological field, we don't routinely dichotomize cancer management, perhaps the best example is bladder cancer management where 85% of patients are initially treated with a bladder preservation approach, as a diagnosis of high-risk transitional cell carcinoma does not equate to radical surgery. However, in prostate cancer the lack of color derives in our opinion from two consequential factors: 1 - How we make the diagnosis - *transrectal random* biopsy; and 2 - *Multifocal* biology of most prostate cancers. The former is by far where our patients and we could use some improvement (20). For starters, the random nature of the biopsy denies reliable precision. The transrectal approach is not applicable for optimal management.

The advance in prostate imaging has led to better recognition and imaging characterization of prostate cancer risk. MR fusion biopsies have emerged to deliver certainty on cancer location and extent. However, most of these techniques employ a transrectal technique, in our view a terrible flaw, and significant contributor to possible harm associated with prostate cancer diagnosis. However, there is an approach to sampling the prostate that is much safer, reliable and opens the door to partial prostate treatment: the transperineal approach. A few years ago, the concept of performing in office transperineal biopsies or treatments was considered non-sense or impossible. Currently, that is not the case; we have demonstrated this with over 1,015 of the procedures in the last 3 years performed using a local anesthesia block (21).

Thus, diagnosis prostate cancer with Transperineal MR Fusion provides for precise knowledge not just of location and extent, but to open the next frontier - the color box - for management: multifocal targeted partial gland ablation.

Some are calling "super-active surveillance" a partial gland ablation (22), we don't necessarily agree this might be the precise term. However, we do with the notion that alternatives are needed to fill the gap between the yin and yang - traditional AS vs. radical treatment. Today there are many energy options available to deliver partial cancer ablation, such as: cryoablation, high-intensity focused ultrasound (HIFU), radiofrequency ablation (RFA), laser ablation, irreversible electroporation (IRE), microwave ablation, photodynamic therapy and convective water vapor.

In our view, any attempt of intervention to the prostate must achieve the following characteristics: 1 - An extremely favorable adverse event profile, thus adverse events are rare, 2 - It must not burn any bridges, thus must not increase significantly the difficulty of radical surgery, shall the patient needed in the future and/or must increase adverse event profile of radiation, 3 - Convalescence from the procedu-

re must be fast, carrying minimal interference with routine life activities, 4 - It should preserve prostate function, thus ejaculation shall be a measurable outcome as be erectile activity, and 5 - Urinary function shall exhibit improvement or no change, with no impact on urinary continence. When it comes to oncological outcomes, ablated cancer control must be demonstrated with tissue, we believe is imperative that patients receive a 1 year follow-up biopsy of ablated areas. Other oncological outcomes to consider include risk of conversion and freedom from androgen deprivation along with classic oncological measures as metastasis-fee survival, cancer specific and all cause survival. Currently, it's impossible to gauge all these outcomes and particularly difficult to compare ablation techniques, given the absence of high--quality and long follow-up studies in the literature (23-25). That is why we call this coming approach the next frontier.

Among the currently employed partial ablation techniques, cryotherapy and HIFU are the ones leading the race. Interestingly however, VTP is the only energy source studied in a multicenter, randomized, controlled phase III trial versus AS. VTP was superior in reducing presence of higher-grade cancer on biopsy (16% vs 41% Gleason 7), reducing chances of radical therapy (25).

Most ablation techniques focus in a zone, or area, some even consider the entire lobe. The argument against these approaches is raised by the multifocality of prostate cancer and what represents or conforms the index lesion. A notion that gas gained traction suggest that cancer related outcomes would derive from the index lesion and not by concomitant indolent tumors that may coexist at the time of diagnosis, as these are commonly low volume Gleason 3+3 (25, 26). Supporters of the index lesion highlight that these are the cancer lesions exhibiting highest Gleason scores and thus harbor incremental potential for local spread, recurrence, resistance and/or metastasis (27-30). However, certain ablation approaches such as Cryoablation and IRE portend advantages addressing multifocality making the theory of the index lesion irrelevant (20).

As mentioned before, the transperineal approach provides direct access to the prostate gland. No wonder the original radical prostatectomy began with a transperineal approach. However, the perineum is hindered by a perception of a need for general anesthesia. We would argue that the anesthesia need is dependent of the technique or energy to be used rather than by the anatomy. Since 2014, as we developed our technique to block the perineum we have performed 1,233 transperineal MR fusion prostate biopsies, and 578 transperineal MR fusion target prostate cancer cryoablations in the office setting under local anesthesia. Safety is the most significant advantage of this approach. We published some of our results and they show an adverse event profile under 3%, most low grade, such as urinary retention. Importantly, post biopsies or cryoablation admission are extremely rare (21).

Moreover, Bianco et al. recently provided with emerging data on MRI Fusion Target Cryoablation as a novel implementation of targeted partial gland ablation. The procedure was performed on 348 patients. Their median age was 71 and 218 had at least 1 year of follow--up. In this series, the median PSA decline was 30% and 164 patients had a follow up prostate fusion biopsy reportedly negative in 109 (66%). Of the positive biopsy patients, 38 were re-treated with 7 patients converted to surgery and 8 to radiation (31).

We have tested our transperineal MR Fusion approach with other energy devices such as needle RFA and circling RFA, while we have done so on limited numbers they seem to be well tolerated by patients and we envision a role in partial gland ablation. We have also tested IRE MR Fusion, however, it requires general anesthesia and that by it self put the energy device as does with HIFU at a different level in term of harms from general anesthesia.

We believe that what's being called "super-active surveillance" or our preference "precise multifocal partial gland ablation" is the next frontier for physicians and patients. The legacy of the randomized trials (AS vs. intervention) is our much profound understanding of the harms associated with intervention along with its limited benefits. Treating the cancer while preserving organ function if where the future is, AS is a good compromise given the impressions associated

with traditional prostate cancer diagnosis, however, we must do better.

Technology advantages, along with critical thinking will serve as our fundamental tools to continue to advance in our quest to deliver better oncological and functional outcomes for our prostate cancer patients. Furthermore, the ablation immunology understanding is underway and preliminary evidence that supports prostate partial ablation vaccine potential by immune system boost has awarded 2018 American Urological Association best poster and warrants future investigations (32).

CONFLICT OF INTEREST

None declared.

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Super active surveillance for low-risk prostate cancer | *Opinion: No*

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Keywords: Prostatic Neoplasms; Risk Reduction Behavior; Watchful Waiting; Therapeutics

INTRODUCTION

Prostate cancer (PCa) is diagnosed in over 170,000 men in the United States each year (1). While this makes PCa one of the most common solid malignancies in men, the mortality is low and most men die from unrelated causes (1). In fact, almost half of men with screening detected and localized PCa are considered candidates for deferred treatment or active surveillance (AS) (2). To decrease the morbidity associated with definitive therapy, many providers recommend AS for those with very-low (VLR), low risk (LR) disease and in selected favorable, intermediate risk (IR) PCa (3-5).

The use of AS has been steadily increasing and is supported by large cohort studies showing 98-100% PCa specific survival rates (6, 7). While the recommended follow-up for AS varies, safety is predicated on close surveillance with predefined thresholds for treatment based on identification of cancer progression yet still curable disease. In the largest published AS cohort of 993 men with median follow-up of 6.4 years, 10-year cancer specific survival (CSS) was 98.1%. However, 27% of these patients ultimately underwent surgery for indications ranging from prostate specific antigen (PSA) progression, biopsy Gleason score progression or patient preference. While this cohort included mostly younger men with LR disease (Age <70, cT1/T2a disease, PSA <10ng/ml), they also included patients older than 70 with Gleason 3+4=7 or lower disease, such that 20% had IR (6). A separate analysis of this cohort by Musunuru et al. showed that while only 3% of patients developed metastases, metastasis free survival (MFS) was significantly lower in the IR as compared to the LR group (84% vs 95%, p=0.001) (8). Another separate cohort analysis by Yamamoto et al. showed a significantly higher risk of 15-year PCa mortality (PCM) for higher Gleason score disease (HR of 4.0 for Gleason 3+4=7 vs Gleason 3+3=6 and HR 10.5 for Gleason 4+3=7 vs Gleason 3+3=6) (9). The PROTECT trial randomized 1643 patients with localized PCa into AS (n=545), definitive treatment with radical prostatectomy (RP; n=553) or radiation therapy (RT; n=545). There was no difference in PCM amongst the 3 groups (p=0.48), however, of those 17 patients who passed away, 8 were in the AS group (5/8 with IR disease), 5 in the RP group and 4 in the RT group. The rate of disease progression and development of metastases was significantly higher in the AS group as compared to RP or RT (112 vs 46 vs 46 men, respectively; p<0.001) (10).

Despite a certain subset of patients who seem to do worse on AS, concerns with morbidity from definitive treatment have led experts to recommend a broadening of the indications for AS and to include selected patients with low volume IR disease (3, 5, 11, 12). As the indications for AS expand, certain patients may wish to be even more "active" in their surveillance. In 2018, Bloom et

al. proposed the concept of "*Super-Active Surveillance*" (*SAS*), which they defined as focal therapy of an index lesion in order to alleviate concerns of disease progression or ultimate need for definitive treatment (13). While studies have shown the feasibility of ablative techniques, the use of *SAS* remains a work-in progress with controversy regarding the ideal candidate, appropriate follow-up and triggers for more definitive treatment. As it stands, *SAS* should only be performed in the hands of well-experienced providers, ideally as part of an investigational study. Herein, we explore the rationale behind SAS and address the lingering but significant questions that require answering before adoption of this as a mainstream approach.

Multiparametric MRI and the changing paradigm in prostate cancer diagnosis

The diagnosis of PCa has classically been via systematic ultrasound guided biopsy. However, this method under stages 30% of men with PCa (14-18). This is thought to be due to under sampling or poor visualization of hard to reach areas such as the apex or anterior zones. Multiparametric magnetic resonance imaging (mpMRI) has emerged as an important diagnostic tool in PCa as it allows more accurate sampling of the prostate so that clinicians will identify more clinically meaningful PCa while avoiding overtreatment of clinically insignificant disease (19, 20). The enhanced ability of mpMRI to detect significant disease comes from mpMRI guided biopsy techniques where suspicious lesions (not visible on US) are targeted during the biopsy (21, 22). The use of mpMRI is now recommended by guideline panels in patients considering AS but with suspicion of significant cancers (3-5).

While mpMRI-guided targeted biopsy is now the preferred approach, some have even proposed an extended role for mpMRI as a replacement for biopsies in those patients on AS (23-26), especially as this image modality has also demonstrated superior detection of progression compared to other markers such as PSA and digital rectal exam (26). However, data supporting the practice of mpMRI as a replacement for repeat biopsy come from single centers that are well experienced with the use of this image modality. Interpretation should come with caution especially as mpMRI may miss up to 15% of clinically significant tumors. The reading of mpMRI requires specially trained genitourinary radiologists and academic centers with more experience are better equipped for standardization of care and subsequent biopsies or treatment (27). Margel et al. found an 83% positive predictive value and 81% negative predictive value for mpMRI in reclassifying patients who no longer met criteria for AS (23). A recent study by Panebianco et al., included 1,255 men with negative mpMRI who were treated at a tertiary referral center. A prior negative biopsy had been performed in 596 men and 659 were biopsy naïve. These men were followed for a minimum of 2 years and freedom from any PCa was 94% overall. At 4 years, the freedom from any grade prostate cancer was 84% for those who were biopsy naïve and 96% in those with a prior negative biopsy (28).

Thus, mpMRI clearly improves detection of prostate cancer, but systematic random biopsies are still needed to prevent a missed cancer diagnosis in those at risk but with negative mpMRI (29). Certainly, larger prospective multi--institutional studies are needed in those with negative imaging. In those with positive imaging however, mpMRI guided, targeted biopsy not only improves detection but also may serve as a useful guide for minimally invasive image--guided treatment (13).

Focal ablation: feasible but safe?

The acceptance of image-guided diagnosis in PCa has spawned the era of image--guided treatment, also known as focal therapy. Focal therapy is defined as the specific targeting and ablation of the malignant target of the prostate while leaving benign tissues intact. Methods of ablation vary and include cryotherapy, high intensity focused ultrasound (HIFU), radiofrequency ablation, laser ablation, irreversible electroporation, microwave ablation, photodynamic therapy and water vapor therapy (30). Feasibility of each treatment has been shown, but level one evidence is lacking as studies consist mostly of single center cohorts without long-term follow-up (13).

Focal therapy is based on the hypothesis that an index lesion, drives cancer related outcomes (31-34). However, PCa is known to be a multifocal disease with unilateral disease occurring in only 20-30% of cases (33-35). Just as negative mpMRI may miss disease, focal therapy has the potential to miss cancer and risk progression. Before focal therapy or SAS can be considered a safe option for patients, the ideal candidate, follow-up and definition of treatment failure must be defined.

The ideal patient for focal therapy is still debated without consensus or long-term data. Gill et al. demonstrated the safety of focal therapy in men with LR PCa (as defined by Gleason score 3+3=6, cT2a, PSA ≤10). They compared AS or focal therapy with targeted photodynamic therapy in 413 men and found a lower conversion to radical therapy in the ablation group compared to the AS group (24% vs 53% at 4 years, HR 0.31, 95% CI 0.21-0.45). Cancer progression rates were also lower in the ablation group (HR 0.42, 95% CI 0.29-0.59) (36). The European Association of Urology has put forth a position statement on focal therapy acknowledging that men with low-risk disease are good candidates as most reports have included men with Gleason 3+3=6 disease. However, those with IR risk disease (Gleason ≤4+3) may be considered for focal therapy just as they are considered for AS (37).

Gland and tumor specific variables must be considered as well. For example, the ideal gland size for HIFU is 40 gram and must be without calcifications that may interrupt ultrasound wave transmission (38). Truesdale et al. evaluated patient selection criteria for unilateral cryoablation and they found that pre-treatment PSA, Gleason score, number of cores positive and total tumor length were associated with biochemical and pathologic disease progression (39).

The appropriate follow up for those on SAS must be defined such that treatment failure requiring conversion to more radical therapies can be reliably predicted. Biochemical recurrence (BCR) is a primary endpoint in predicting treatment failure after RP or RT, but no universal criteria for BCR exist after focal therapy of the prostate. While residual disease may exist after focal therapy and potentially can lead to progression, PSA has not been shown to be a good predictor of this risk (40). Viable and benign prostate tissue will continue to produce PSA. Moreover, PSA kinetics in a partially ablated gland differ from those following whole gland ablation, RP or RT (41). The results of repeat biopsy due to PSA based changes are highly variable as studies have found residual disease in 8-45% of cases (39, 42, 43). Routine biopsy performed one year after ablation similarly shows variable rates of residual disease with disease in 0-26% of cases (40, 41, 44, 45). Some have proposed a mpMRI based method of detecting recurrent disease after focal therapy (46) but an inability to define true treatment failure remains: is it any residual disease within the prostate, any clinically significant disease or only clinically significant disease within the ablation zone? Certainly, stronger evidence is needed at this time.

The decision to discontinue AS and proceed to more aggressive treatments currently depends on deterioration of inclusion criteria and not just worsening of mpMRI features or development of new lesions on their own (5). Given the considerable uncertainties in follow--up after focal therapy and outcomes of surgery or radiation after failed ablation, the EAU recommends that patients should be treated with focal therapy only within the context of a clinical trial using predefined criteria (37).

CONCLUSIONS

Paradigm shifts are underway in the management of prostate cancer. AS is a safe and recommended option for patients with LR disease and a favorable risk IR disease. Concerns over disease progression and eventual need for definitive treatment have driven patient interest in alternative options to AS that still avoid the morbidity or surgery of radiation.

The use of mpMRI and fusion biopsy has greatly enhanced urologists' ability to diagnose prostate cancer and to determine patients' candidacy for AS. While focal therapy of these lesions is technically feasible, we are in need of larger, prospective studies with adequate follow up in order to determine true oncologic outcomes. Significant questions remain regarding the appropriate candidate for SAS, follow up as well as triggers for conversion to more definite therapy.

While patient driven excitement may influence urologists to pursue SAS, its use should be reserved for high volume centers with a dedicated focal therapy team under a cautious surveillance protocol. While an exciting option for consideration, SAS should be considered as an investigational option at this time.

CONFLICT OF INTEREST

None declared.

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Role of Adiponectin in prostate cancer

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ABSTRACT

Obesity is defined as a chronic and excessive growth of adipose tissue. It has been associated with a high risk for development and progression of obesity-associated malignancies, while adipokines may mediate this association. Adiponectin is an adipose tissue-derived adipokines, with significant anti-diabetic, anti-inflammatory, anti-atherosclerotic and anti-proliferative properties. Plasma adiponectin levels are decreased in obese individuals, and this feature is closely correlated with development of several metabolic, immunological and neoplastic diseases. Recent studies have shown that prostate cancer patients have lower serum adiponectin levels and decreased expression of adiponectin receptors in tumor tissues, which suggests plasma adiponectin level is a risk factor for prostate cancer. Furthermore, exogenous adiponectin has exhibited therapeutic potential in animal models. In this review, we focus on the potential role of adiponectin and the underlying mechanism of adiponectin in the development and progression of prostate cancer. Exploring the signaling pathways linking adiponectin with tumorigenesis might provide a potential target for therapy.

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INTRODUCTION

Prostate cancer (PC) recently became the second most prevalent cancer afflicting men, and the fifth leading cause of cancer related death throughout the World (1, 2). Age, familial history, smoking, sedentary lifestyle and overweight are all factors in the pathogenesis of PC. Of note, obesity is well known as an increased risk for several cancers (including colon, ovary, breast, esophagus and pancreatic), also for PC (3, 4). The links between obesity and PC are complicated. Three possible mechanisms are proposed to help explain the association between obesity and the increased risk of PC: the insulin / insulin-like growth factor-1 (IGF-1) axis, sex hormones and adipokines signaling (5, 6). Adiponectin (APN), an adipocyte-secreted adipokine, operates in the maintenance of many physiological functions, having potential benefits in the prevention of certain diseases. It mainly regulates inflammation and influences glucose and lipid metabolism through its insulin sensitizing effects (7, 8). Recently, APN was proved to be one of the mediators in the development and progression of several types of obesity-associated cancers (9). In this report, we summarized recent findings on the potential role of APN and the underlying mechanism of APN in PC. In addition, the clinical values of APN for PC patients will also be highlighted.

Adiponectin and its receptors

Adiponectin, also called Acrp30, is a 28-30-kDa adipokine produced mainly by adipose tissue. Full-length APN (fAPN) consists of an N--terminal signal sequence, a short hypervariable region, a collagen-like domain and a C-terminal globular domain (10, 11). Pre-secretion, post-translational processing generates trimers, hexamers, and high molecular weight (HMW)-APN. HMW-APN appears to be the physiologically most relevant and dominant form in plasma (10). Fruebis et al. (11) identified the fourth fraction of APN in the plasma, the globular domain of APN (gAPN), which is generated by the proteolytic cleavage of fAPN.

Normal plasma APN levels range from 5 to 30 µg / mL, accounting for up to 0.05% of total plasma proteins in humans (11). Despite the fact that APN is produced mainly by adipose tissue, its serum concentration is reversely correlated with the body mass index (BMI) (12). One possible explanation of the reduced APN levels in obesity may be caused by the enhanced production of proinflammatory cytokines, in particular, by TNF-α, IL-6. Another explanation that serves to downregulate APN expression is endoplasmic reticulum (ER) stress resulting from obesity. In addition, it is demonstrated that there is a negative feedback of APN on its own production during the development of obesity (12). APN plasma concentration was found to be sex dependent, with there being a higher serum concentration in women than in men (12).

Although produced by adipose tissue, APN functions via the specific receptors, AdipoR1 and AdipoR2. Both these receptors contain seven transmembrane domains with the C-terminus inside the cells and the N-terminus outside (13). Specifically, AdipoR1, ubiquitously expressed and highly expressed in skeletal muscle, possess a high-affinity for gAPN and a low affinity for fAPN. In contrast, AdipoR2, predominantly expressed in the liver, binds both gAPN and fAPN with an intermediate affinity (13). T-cadherin has been successively discovered as a third receptor for APN, with a high affinity to HMW-APN (14). It is an atypical glycosyl phosphatidylinositol-anchored cadherin, located on the cellular surfaces of endothelial, epithelial, and smooth muscle cells (14). Because T-cadherin lacks both transmembrane and cytoplasmic domains, it is considered to have no effect on APN cellular signaling or function. Its main role is thought to act as an APN-binding protein, rather than a receptor.

Adiponectin and prostate cancer

Adiposity has been consistently associated with an increased risk of progression of PC, but APN is inversely related to the degree of adiposity. It seems that plasma APN should be reduced in PC patients. Goktas et al. (15) was the first to report that serum APN levels were significantly lower in patients with PC than in the BPH group or in healthy controls. In addition, APN levels were negatively associated with histological grade and disease stage. Next, a study of 300 Greek men by Michalakis et al. (16) revealed a significantly reduced risk of PC with higher plasma APN concentrations. In line with this, APN receptor levels are likewise lower in resected PC tissues. Several studies have supported the inverse association between APN and risk of PC or high-grade PC (17-21). Therefore, these findings indicated the potential role of APN in the suppression of carcinogenesis. However, as HMW-APN is the most active form of APN, Medina EA et al. (22) evaluated the relation between HMW-APN and PC, and found that only HMW-APN decreased the risk of PC in obese man. In 2006, Baillargeon et al. (23) found no correlation between APN levels and the development of PC. Furthermore, they found no association of PC with BMI, leptin and IL-6. In 2014, a study by Stevens et al. (24) also revealed APN is not associated with risk of aggressive PC. Thus, the precise role of APN in the development of PC remains elusive. In 2015, using a cross-sectional study, Ikeda A et al. (25) detected PC by prostate-specific antigen (PSA)-based screening and firstly demonstrated a significant and positive correlation between APN levels and PSA levels. One explanation was the proportion of obese men in the study was extremely low, another one was maybe the increased APN being a protective response against tumor progression, and the third one was they did not evaluate HMW-APN in this study. Finally, Liao Q (26) performed a meta-analysis of numerous stu-

dies and concluded that patients with PC markedly had lower APN levels than controls, they also found that decreased concentration of APN was associated with a significantly greater risk of PC.

Given that APN encoding gene (ADIPOQ) and its receptor (ADIPOR) are highly polymorphic and carry several single nucleotide polymorphisms (SNPs), the genetic variants of ADIPOQ and ADIPOR might affect PC risk. In a study with 1,286 cases and 1,267 controls, Dhillon P et al. (27) found four SNPs of ADIPOQ were significantly associated with PC risk, two of which were also associated with plasma APN concentration. Furthermore, Kaklamain et al. (28) conducted a study that also noted the effects of genetic variations in ADIPOQ and ADIPOR1 gene on PC. Conversely, two other studies demonstrated no associations in candidate SNPs and PC risk (29, 30). Since these results were inconsistent and insufficient, an updated meta-analysis performed by Hu et al. revealed that ADIPOQ rs 2241766 and ADIPOR1 rs 10920531 variants were identified to be correlated with increased risk of PC. On the contrary, ADIPOR1 rs 2232853 variants were associated with decreased risk of PC (31). The identified polymorphisms might help prediction of prevalence and prognosis of PC, as well as generation of novel targeted therapies.

The relationship between APN receptors and PC has also been examined by many investigators. Mistry T et al. (32) firstly showed AdipoR1 and AdipoR2 expressed both in benign and adenocarcinomatous prostate tissue by immunohistochemistry analysis. The presence of the receptors expression suggested that APN binding to its receptors may mediate prostate physiology and pathologic changes. In 2007, Michalakis K et al. (16) showed that malignant prostate tissue samples reduced expression of APN receptors compared with benign prostate tissue. In line with APN receptors, the serum APN concentrations in patients with PC were lower than those in controls, which led to the hypothesis that receptor downregulation in PC would promote cancer progression. However, another study conducted by Rider JR et al. (33) revealed that there was a positive relationship between AdipoR2 and PC development. The relationship between APN receptors expression and carcinogenesis is somewhat controversial, therefore more studies are needed to elucidate the link between APN receptors and PC. The results of epidemiological studies of the association between APN levels and PC are summarized in Table-1.

Potential mechanisms of adiponectin in prostate cancer

Recent advances suggested that APN plays a role in carcinogenesis through numerous mechanisms including inhibiting proliferation and inducing apoptosis (19, 20, 34-42). Recent studies have shown that activation of the adenosine monophosphate-activated protein kinase (AMPK) is a key part of the signaling cascade downstream of APN receptor (20, 34-36). The proteins downstream of AMPK included tuberous sclerosis protein 2 (TSC2), the mammalian homologue of the target of rapamycin (mTOR), vascular endothelial growth factor A (VEGF-A) and fatty acid synthase (FAS), all of which are involved in the regulation of cell proliferation. In PC-3 cells, activation of AMPK by APN is associated with reduction in mTOR activation, which reduces protein translation and inhibits cell growth (34). In this study, when siRNA reduced AMPK level, APN-induced growth is significantly inhibited.

Another study of modification of APN levels in PC-3 cells supported that APN activates AMPK / TSC2 to inhibit mTOR-mediated VEGF--A activation and to inhibit cancer neovascularization (20, 35). In addition, AMPK prevents fatty acid synthesis by downregulation FAS, then inhibited cell growth and induced apoptosis in LNCaP cancer cells (36).

Signal transducers and activator of transcription 3 (STAT3) appears to be a key regulator for cell proliferation and apoptosis. Both fAPN and gAPN can stimulate JNK activation, then drastically suppress STAT3 activation in DU145 cells, suggesting that JNK and STAT3 may constitute a universal signaling pathway to mediate APN's pathophysiological effects on PC (37).

APN also has anti-proliferation effects on many cell lines including PC3, DU145 and LNCaP PC cells (38, 39). APN induced cell cycle arrest of prostatic epithelial and stromal cell lines through

Table 1 - Recent Studies showing the association between APN concentrations and risk of PC.

Reference	Sample numbers	APN levels / OR	Comments / Conclusion	Other findings	TS
Goktas S (15)	30 PC 41 BPH 36 Con	5.3 ± 1.6 µg / mL 14.5 ± 4.4 µg / mL 16.2 ± 4.1 µg / mL	APN concentrations are lower in PC than BPH or in control subjects	APN are negatively associated with the histologic grade and disease stage of PC	CC
Michalakis K (16)	75 PC 75 BPH 150 Con	7.4 ± 5.0 µg / mL 11.5 ± 6.4 µg / mL 12.8 ± 8.0 µg / mL	Higher plasma APN concentrations are associated with a reduced risk of PC	AdipoR1 and AdipoR2 in cancerous were weaker expressed compared with healthy prostate tissue	CC
Schenk JM. (17)	698 BPH 709 Con	OR = 0.43	High APN concentrations were associated with reduced risk of BPH	Neither C-peptide nor leptin was associated with BPH risk	NCC
Li H (18)	654 PC 644 Con	Q1: 2.7 µg / mL Q3: 6.3 µg / mL Q5: 13.3 µg / mL	Higher APN concentrations have a lower risk for developing high-grade or metastatic cancer	Leptin was unrelated to PC risk or mortality	NCC
Tan W (19)	96 PC 15 BPH	Low level of APN BPH: 1of 15 (6.7%) GS <7: 6of 27 (22%) GS = 7: 18of 26 (69%) GS > 7: 32of43 (74%)	APN was significantly decreased in PC compared with that of BPH tissues Decreased APN level was significantly associated with high GS	APN may function as a tumor suppressor through inhibiting EMT of PC cells.	CC
Medina EA (22)	228 PC 239 Con	OR = 0.62	Only HMW APN decreased the risk of PC in obese man	HMW increased the risk of PC in normal and overweight men	NCC
Baillargeon J (23)	125 PC 125 Con	17.9 ± 0.6 µg / mL 19.9 ± 13.2 µg / mL	APN was not significant associated with PC risk	BMI was not associated with incident PC	NCC
Stevens VL. (24)	272 PC 272 Con	OR = 1.11	APN was not associated with risk of aggressive PC	C-peptide was not associated with risk of aggressive prostate cancer	NCC
Ikeda A. (25)	24 PC 2817 Con	9.96 µg / mL 7.64 µg / mL	APN was significantly and positively associated with PSA levels	High APN increased the Incidence of low- or mediate-risk PC in obese man	CS

APN = adiponectin; **PC =** prostate cancer; **BPH =** benign prostatic hyperplasia; Con = Control; **TS =** type of study; **CC =** case - control; **NCC =** nested-case-control; **CS =** cross-sectional; OR = odds ratio; Q5 = Highest quintile; **Q3 =** intermediate Quintile; **Q1 =** Lowest Quintile; **GS =** Gleason score; **PSA =** prostate-specific antigen.

the downregulation of cyclinD1 and PCNA, which attenuated the growth factor-mediated proliferation. Additionally, APN induced apoptosis by increasing caspase 3, Bax expression and downregulation of Bcl2 (40).

Furthermore, APN significantly inhibits cell proliferation induced by leptin. Different leptin / adiponectin ratios resulted in varying inhibitory effects on PC cells, indicating the balance between APN and leptin might effectively modulate PC cell growth. APN can attenuate the adverse effects of leptin and inhibit LNCaP and PC3 proliferation via modulation of p53 and bcl-2 expression (41), hence the balance of leptin and APN may be important in driving obesity-related PC progression.

Oxidative stress (OS) is a key event in the initiation, development and progression of PC. APN increased cellular anti-oxidative defense mechanisms and inhibited OS via increasing NADPH oxidase NOX2 and NOX4 expression in human 22Rv1 and DU-145 PC cell lines (42). Despite an increasing accumulation of experimental data, the mechanisms underlying the anti-proliferative and tumor-suppressing effects of APN are still not fully understood, more studies are needed. The role of APN in PC is summarized in Figure-1.

Clinical values of Adiponectin for prostate cancer patients

Based on the signaling pathway conducted by APN and its receptors, APN might represent a promising therapeutic target. Currently, the administration of APN or direct antagonist has not been reported in the literature for the treatment of human cancers. A strategy for the future treatment of PC patients with hypoadiponectinemia may include the upregulation of APN levels, APN receptors, or the development of APN receptor agonists.

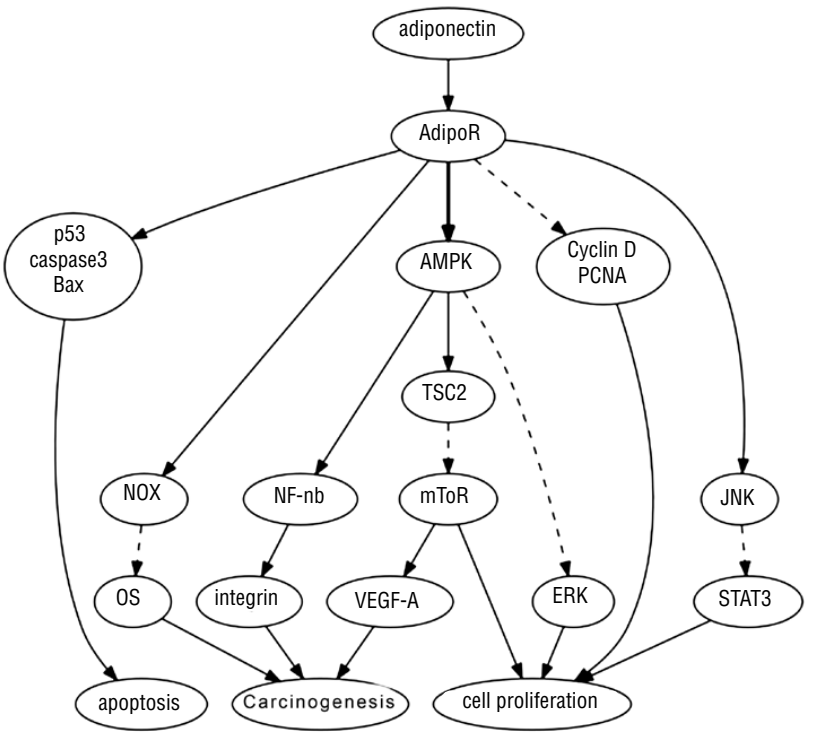
Tangible benefits may come from the anti-diabetic drug Metformin. Metformin partially mimicked APN action and activate AMPK signaling in PC-3 cells, with reduction of mTOR activity thus inhibition of cell growth, suggesting that Metformin might have particular value in attenuating the adverse effects of hypoadiponectinemia on PC (34). Metformin therapy has been correlated with reduced risk of prostate cancer in Caucasian / white men with diabetes (43) and with a survival benefit after diagnosis (44). These results underscore the importance for further studies to evaluate metformin in PC. Plasma APN levels can also be upregulated by thiazolidinediones (TZDs), such as pioglitazone, rosiglitazone, a class of PPAR-γ agonists and medicine used in the treatment of type II diabetes (T2D). Clinically, Metformin and thiazolidinedione therapy improved survival of diabetics prostate cancer patients (45).

Down-regulation of APN in PC tissues and LNCaP cells owing to highly methylation in its promoter, and 5-AZA restored its expression in vitro. Thus, methylation of APN promoter may be a key factor for evaluation of PC, and 5-AZA may be a promising stimulator of APN (19). Zorn CS et al. (46) reported that 5-AZA improves survival in the transgenic adenocarcinoma of the mouse prostate (TRAMP) model.

Previous research suggested that diet pattern as well as physical activity might increase expression of APN and delay disease progression in PC patients (47, 48). Hence, moderate physical exercise, reduction of body fat, associated with restriction of calories in diet are recommended for obesity-related prostate cancer prevention.

Another potential therapeutic molecule is the APN receptor agonist. Agonists have been developed and tested to treat multiple diseases related to hypoadiponectinemia, diabetes and other malignancies (49, 50). ADP355, a first-in-class APN receptor agonist, restricted proliferation in several APN receptor-positive cancer cell lines, and suppressed the growth of established tumors by 31% in vivo (49). AdipoRon, with similar effects to APN, increased apoptosis while inhibiting pancreatic cell proliferation and colony formation. In vivo, treatment of mice with AdipoRon inhibits orthotopic pancreatic tumor growth (50). APN receptor agonists may represent novel therapeutic strategies for PC in future.

Figure-1 - Signaling pathways of adiponectin in prostate cancer cells.



JNK = c-Jun N-terminal kinase; **STAT3 =** signal transducer and activator of transcription; **AMPK =** AMP-activated protein kinase; **TSC2 =** tuberous sclerosis complex 2; **mTOR =** mammalian target of rapamycin; **NF-KB =** nuclear factor-KB; **NOX =** NADPH oxidase; **OS =** oxidative stress; ↓ indicates stimulation; ↓ indicates inhibition.

CONCLUSIONS

Numerous studies supporting the notion that APN acts as a protective and safe factor to prevent progression of PC, but few studies may indicate otherwise. We summarized the mechanisms underlying the anti-proliferative and tumor-suppressing effects of APN specifically in PC without reiterating other types of cancers. The signaling pathways linking APN with tumorigenesis involve several key molecules, including AdipoRs, AMPK, JNK, NOX, NF-κB, and so on, thus providing potential drug targets for the future. Based on the beneficial effects induced by APN, future efforts can focus on increasing APN and its receptors levels in response to PC. Since APN exerts pleiotropic effects on different tissues and exists as a high serum concentration protein, the main role of APN should be regulation of metabolism, not necessarily to act as an anti-cancer hormone. We must consider many other risk factors for PC with a lower level of APN, which could help develop better approaches for the treatment and prevention of all men with PC. Moreover, further research is warranted to better understand the pathophysiological role of APN in obesity and obesity--related PC, and elucidate the potential clinical application in humans.

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CONFLICT OF INTEREST

None declared.

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The TNM 8th edition: Validation of the proposal for organ - confined (pT2) prostate cancer

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ABSTRACT

Purpose: The 8th edition of the TNM has been updated and improved in order to ensure a high degree of clinical relevance. A major change in prostate includes pathologically organ - confined disease to be considered pT2 and no longer subclassified by extent of involvement or laterality. The aim of this study was to validate this major change.
Materials and Methods: Prostates were step - sectioned from 196 patients submitted to radical prostatectomy with organ confined disease (pT2) and negative surgical margins. Tumor extent was evaluated by a semiquantitative point count method. The dominant nodule extent was recorded as the maximal number of positive points of the largest single focus of cancer from the quadrants. Laterality was considered as either total tumor extent (Group 1) or index tumor extent (Group 2). Time to biochemical recurrence was analyzed with the Kaplan - Meier product limit analysis and prediction of shorter time to biochemical recurrence with Cox proportional hazards model.
Results: In Group 1, 43 / 196 (21.9%) tumors were unilateral and 153 / 196 (78.1%) bilateral and in Group 2, 156 / 196 (79.6%) tumors were unilateral and 40 / 196 (20.4%) bilateral. In both groups, comparing unilateral vs bilateral tumors, there was no significant clinicopathological difference, and no significant association with time as well as prediction of shorter time to biochemical recurrence following surgery.
Conclusions: Pathologic sub - staging of organ confined disease does not convey prognostic information either considering laterality as total tumor extent or index tumor extent. Furthermore, no correlation exists between digital rectal examination and pathologic stage.

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INTRODUCTION

The 8th edition of the TNM has been updated and improved in order to ensure a high degree of clinical relevance (1, 2). Major changes in prostate include: 1) Pathologically organ - confined disease is now considered pT2 and is no longer subclassified by extent of involvement or laterality; 2) Tumor grading now includes both the Gleason score (as in the seventh edition criteria) and the grade group (introduced in the eighth edition criteria); 3) Prognostic stage group III includes select, organ - confined disease based on prostate - specific antigen and Gleason / grade group status; and,

4) Two statistical prediction models are included in the staging manual.

The aim of this study was to validate the major change 1 of the 8th edition of the TNM. We evaluated the tumor in either its total extent or exclusively the index tumor extent. To the best of our knowledge there is no other study considering index tumor extent in sub - staging. Furthermore, we studied the possible correlation between digital rectal examination and pathological stage.

MATERIALS AND METHODS

This retrospective study was based on 196 consecutive patients in a time period from 1997 to 2015 with organ confined prostate cancer (pT2) and negative surgical margins treated with retropubic RP by 1 surgeon (UF). We compared the biochemical recurrence following surgery of unilateral (pT2a / pT2b) vs bilateral (pT2c) tumors considering either total tumor extent (Group-1) or index tumor extent (Group-2). Several clinicopathological variables were also studied.

After RP, serum PSA was drawn every 3 months during the first year, every 6 months during the second year, and annually thereafter. No patient of this series had radiotherapy or androgen manipulation before or after surgery. Total serum PSA was measured utilizing previous validated Immulite® PSA kit. Biochemical recurrence following surgery was considered as PSA ≥ 0.2ng / mL according to recommendation of the American Urological Association (3). Patients without evidence of BCR were censored at last follow-up. PSA density was calculated using the pathological weight of the prostate without the seminal vesicles. The present study was approved by the Institutional Committee of Ethics of our Institution.

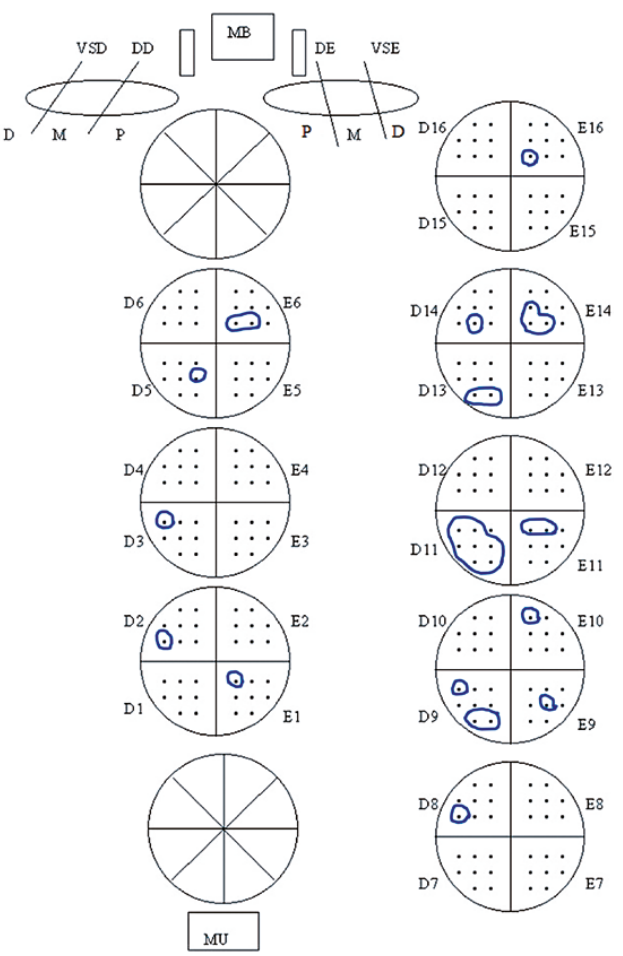
Surgical specimens were step sectioned at 3 to 5 mm intervals and embedded in paraffin. A mean of 32 paraffin blocks was processed. Sections (6 µm) of each block were stained with hematoxylin and eosin. Each transverse section of the prostate was subdivided into 2 anterolateral and 2 posterolateral quadrants. Using the cone method 8 sections from the bladder neck and 8 from the apex were obtained. Each seminal vesicle was sampled with 3 transverse sections: proximal, median, and distal.

Positive surgical margin was defined as cancer cells in contact with the inked specimen surface. Extra - prostatic extension was diagnosed whenever cancer was seen in adipose tissue and, in case of desmoplastic response, when a protuberance corresponding to extension of tumor into peri - prostatic tissue was seen. Seminal vesicle invasion occurred when there was involvement of the muscular coat. RP Gleason grading was stablished according to the 2014 International Society of Urological Pathology (ISUP) consensus conference (4) considering the entire tumor. According to Gleason score the tumors were classified as grade group 1 (≤ 6), grade group 2 (3 + 4 = 7), grade group 3 (4 + 3 = 7), grade group 4 (8), and grade group 5 (9-10). Nodular hyperplasia was considered whenever this pathological finding was in the surgical specimen. Digital rectal examination was recorded as T1c, cT2a / cT2b, and cT2c.

Tumor extent at RP was evaluated by a previously described semiquantitative point count method (5). Briefly, each quadrant of the transverse sections was drawn on paper and contained 8 equidistant points. During microscopic examination of the slides, the tumor area was drawn on the correspondent quadrant on the paper (Figure-1). At the end of examination, the number of positive points represented an estimate of tumor extent but not volume. Each positive point corresponds to 10 - 15% of extent in each quadrant.

Total tumor extent was recorded as the total sum of positive points of all transverse quadrants. Index tumor extent (dominant nodule) was recorded as the maximum number of positive points for the largest single focus of cancer present in the quadrants and not with the highest grade. In Figure-1, total and index tumor extent was recorded as 28 and as 7 positive points, respectively; the tumor is bilateral considering total tumor extent, and unilateral considering index tumor extent. In Group-2, bilateral tumors were considered when index tumor had the same number of positive points on both sides either in adjacent quadrants or not. Even in non - adjacent quadrants, most probably the nodules are not co - dominant. The dominant tumor nodules are rarely symmetrical and mostly will be on one side and part of the nodule will cross the midline. All cases were reviewed by a senior uropathologist (AB).

Figure 1 - Semiquantitative point count method to evaluate tumor extent. In this case, total tumor extent was recorded as 28 positive points. Quadrant D11 shows largest single cancer focus or dominant nodule of all quadrants, recorded as 7 index tumor positive points. The tumor is bilateral considering total tumor extent, and unilateral considering index tumor extent.



Statistical analysis

The data were analyzed using the Qui - square test and Fisher's exact test to compare proportions, the Mann - Whitney test to compare means, Kaplan - Meier product limit analysis for TBCR using the log rank test for comparison between the groups according to laterality, and Cox stepwise logistic regression model was used to identify significant predictors of shorter TBCR. Statistical significance was considered at $p < 0.05$. All statistical analyses were performed using PASW® Statistics 18.0.

RESULTS

Group 1 (total tumor extent)

In this group, 43 / 196 (21.9%) tumors were unilateral and 153 / 196 (78.1%) bilateral.

Clinicopathological Findings

Except for RP Gleason grade on the limit of significance, there was no significant association comparing bilateral vs unilateral tumors (Table-1).

Pathological stage vs. clinical stage by DRE

Only 4 (2.8%) patients were considered cT2c by DRE vs. 153 (78.1%) patients pT2c; and, 18 (41.9%) patients were considered cT2a / cT2b by DRE vs. 43 (21.9%) pT2a / pT2b. Information for clinical stage was missing in 9 patients.

Time to BCR

There was no significant different association with TBCR in Kaplan - Meier estimates. At 5 years of follow-up 69% of patients with unilateral tumors were BCR free vs. 83% with bilateral tumors (log rank p = 0.244, Figure-2) at a mean follow-up of 60 months (median 47, range 3 - 187).

Risk of Shorter TBCR

On univariate Cox analysis, laterality did not significantly predict shorter time to PSA biochemical recurrence after surgery (HR 0.679, 95% CI 0.352 - 1.309, p = 248).

Group 2 (index tumor extent)

In this group, 156 / 196 (79.6%) tumors were unilateral and 40 / 196 (20.4%) bilateral.

Clinicopathological Findings

There was no significant association comparing bilateral vs. unilateral tumors (Table-2).

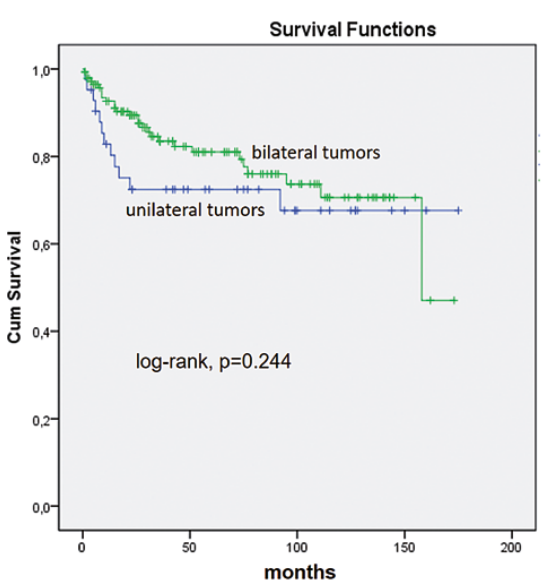
Pathological stage vs. clinical stage by DRE

Only 1 (2.7%) patient was considered cT2c by DRE vs. 40 (20.4%) patients pT2c; and, 15 (40.7%) patients were considered cT2a / cT2b by DRE vs. 156 (79.6%) patients pT2a / p2Tb.

Table 1 - Clinicopathological features of 43/196 (21.9%) unilateral tumors vs 153/196 (78.1%) bilateral tumors by total tumor extent.

Feature	Unilateral tumors	Bilateral tumors	p Value
Mean ± SD age/median (range)	61.95 ± 6.63/62 (46-73)	63.05 ± 6.45/64 (46-76)	0.384 (Mann-Whitney test)
Mean ± SD prostate weight/median (range)	41.47 ± 19.52/38 (15-110)	43.08 ± 24.95/36 (15-185)	0.934 (Mann-Whitney test)
No. nodular hyperplasia (%)			
Neg	9 (20.9)	42 (27.8)	0.435 (Fisher exact test)
Pos	34 (79.1)	109 (78.2)	
Mean ± SD preop PSA/median (range)	8.45 ± 4.60/7.70 (2-20)	7.79 ± 5.12/6.48 (0.60-33)	0.209 (Mann-Whitney test)
Mean ± SD PSA density/median (range)	0.23 ± 0.16/0.20 (0.04-0.85)	0.33 ± 1.56/0.17 (0.03-19.25)	0.135 (Mann-Whitney test)
No. Grade group (%)			
1 (≤6)	29 (67.4)	69 (45.1)	0.057 (Qui-square test)
2 (3+4=7)	10 (23.3)	70 (45.8)	
3 (4+3=7)	3 (7.0)	11 (7.2)	
4 (8)	0 (0.0)	1 (0.7)	
5 (9-10)	1 (2.3)	2 (1.3)	
No. clinical stage (%)			
T1c	25 (58.1)	82 (56.9)	0.543 (Qui-square test)
T2a/T2b	18 (41.9)	58 (40.3)	
T2c	0 (0.0)	4 (2.8)	

Figure 2 - Kaplan - Meier product limit analysis shows time to PSA biochemical progression - free outcome by laterality considering total tumor extent. Cum, cumulative.



Time to BCR

There was no significant association with TBCR in Kaplan - Meier estimates. At 5 years of follow-up 77% of patients with unilateral tumors were BCR free vs. 84% with bilateral tumors (log - rank, p = 0.197, Figure-3) at a mean follow-up of 60 months (median 47, range 3 - 187).

Risk of Shorter TBCR

On univariate Cox regression analysis laterality did not significantly predict shorter time to BCR by index tumor extent (HR 0.571, 95% CI 0.240 - 1.357, p = 205).

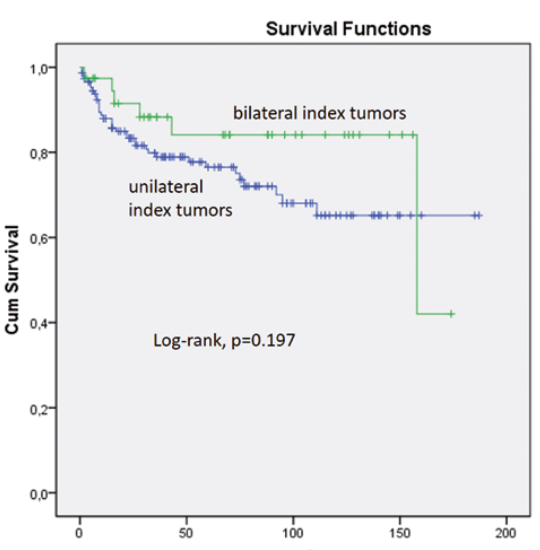
DISCUSSION

Our study validates the TNM 8th edition for organ - confined prostate cancer. Pathologic sub - staging did not convey prognostic information either

Table 2 - Clinicopathological features of 156/196 (79.6%) unilateral tumors vs 40/196 (20.4%) bilateral tumors evaluated by index tumor extent.

Feature	Unilateral tumors	Bilateral tumors	p Value
Mean ± SD age/median (range)	63.05 ± 6.74/64.50 (46-76)	61.85 ± 5.35/62 (52-72)	0.162 (Mann-Whitney test)
Mean ± SD prostate weight/median (range)	42.74 ± 24.15/35.50 (15-185)	42.66 ± 22.76/38.50 (18-130)	0.822 (Mann-Whitney test)
No. nodular hyperplasia (%)			
Neg	39 (25.3)	12 (30.0)	0.550 (Fisher exact test)
Pos	115 (74.7)	28 (70.0)	
Mean ± SD preop PSA/median (range)	8.22 ± 5.33/6.96 (0.60-33)	6.82 ± 3.30/6.35 (0.60-14.60)	0.421 (Mann-Whitney test)
Mean ± SD PSA density/median (range)	0.21 ± 0.15/0.18 (0.03-1.10)	0.18 ± 0.12/0.16 (0.03-0.63)	0.145 (Mann-Whitney test)
No. Grade group (%)			
1 (≤ 6)	79 (50.6)	19 (47.5)	0.461 (Qui-square test)
2 (3+4=7)	63 (40.4)	17 (42.5)	
3 (4+3=7)	12 (7.7)	2 (5.0)	
4 (8)	0 (0.0)	1 (2.5)	
5 (9-10)	2 (1.3)	1 (2.5)	
No clinical stage (%)			
T1c	86 (57.3)	21 (56.8)	0.965 (Qui-square test)
T2a/T2b	61 (40.7)		
T2c	3 (2.0) 1 (2.7)	15 (40.5)	

Figure 3 - Kaplan - Meier product limit analysis shows time to PSA biochemical progression - free outcome by laterality considering index tumor extent. Cum, cumulative.



considering laterality as total tumor extent or index tumor extent. To the best of our knowledge, there is no other study considering index tumor extent in sub - staging. There were no significant clinicopathologic differences by laterality considering either total tumor extent or index tumor extent, and no significant difference for time to biochemical recurrence using Kaplan - Meier product limit analysis as well as prediction of shorter time using Cox stepwise logistic regression.

The multifocality seen in most prostate cancers is one major cause for absence of symmetry between clinical and pathological T2 sub - staging (6, 7) Prostate cancer may be extensive on one lobe (index tumor) and only insignificant on the other side.

There was no correlation between digital rectal examination and pathologic staging. The frequency of bilateral tumors (pT2c) evaluated by

total tumor extent was 78.1% but only 2.8% were considered bilateral (cT2c); for unilateral tumors, 21.9% were pT2a / pT2b and 41.9% cT2a / cT2b. The frequency of bilateral tumors (pT2c) evaluated by index tumor extent was 20.4% but only 2.7% were considered bilateral (cT2c); for unilateral tumors, 79.6% were pT2a / pT2b and 40.7% cT2a / cT2b.

The objective of staging is: 1) to group malignancies with a similar prognosis and therapeutic approach; 2) to perform clinical trials or research studies on homogeneous patient populations; and, 3) to enhance the comparability of clinicopathologic data from hospitals and research groups across the World (8).

In general, pathologic staging (or sub - staging) tries to maintain symmetry with clinical staging (or sub - staging), allowing a direct comparison of both. The clinical staging of prostate cancer is a reflection of the detection methods employed and the sub - staging of clinical stage T2 prostate cancers is largely based on the extent of the abnormality palpated during a digital rectal examination or shown during transrectal ultrasonography in each half of the prostate (8).

The 1997 TNM staging system classified T2 prostate cancers into 2 groups: T2a (unilateral tumor) and T2b (bilateral tumor) (9). In 2002 and in 2009 the TNM staging system returned to the 1992 staging system classifying prostate cancers into 3 groups: T2a (unilateral tumor, involving less than half lobe), T2b (unilateral tumor, involving more than half lobe), and T2c (bilateral tumor) (10, 11).

During a consensus conference sponsored by the International Society of Urological Pathology (ISUP) on handling and staging of radical prostatectomy specimens held in Boston during the 98th meeting of the United States and Canadian Academy of Pathology (USCAP), 65.5% of the attendants answered that the current pT2 sub - staging system should not be used (12). Answering to another question, 63.4% favored to be reduced to two categories based on studies showing that pathological T2b tumor does not exist (13-15).

Several studies have shown that pathologic T2 sub - staging does not convey prognostic information (13, 16-19). This paradox may be apparently explained in part by the fact that clinical criteria used in assessing stage indirectly estimate the chance of under - staging and in this way, they seem to stratify the heterogeneous group of clinical stage T2 patients (8). Smith and Catalona (20) found that the reproducibility of DRE for detecting prostate cancer is only fair among urologists. Probably, most palpable cT2b tumors are already pT2c or T3 disease, explaining why clinical staging has a better correlation with prognosis. Obek et al. (21) reviewed 89 patients with clinically palpable tumors (cT2) to assess whether the clinicians characterization of the disease as unilateral or bilateral by DRE correlated with the final pathology specimen. In 85 patients, a unilateral lesion was suspicious in DRE. The final pathological review revealed cancer on the suspicious side in 82 cases (96%) with tumor confined to the same lobe in only 23 (27%), bilateral disease in 59 (69%) and tumor confined to the contralateral lobe in 3 (4%). On the clinically benign side on DRE, there was a 36 and 31% incidence of extra - prostatic tumor extension and positive surgical margins, respectively.

A limitation of the current study is the small sample size and the relative short time of follow-up. The small sample may reflect the exclusion criteria in our series (stage pT2 and negative surgical margins). Local progression and distant metastases may develop even after 15 years of follow-up (22) however, more than 90% of patients experience recurrence within 5 years after surgery (23). Our point count method evaluates tumor extent but not volume and may not be accurate. Computer assisted analysis is the most precise method for tumor volume evaluation. The point count method ignores vertical tumor dimension but is equivalent to other methods that can be used by pathologists in routine practice (24, 25).

CONCLUSIONS

The findings of the study validate the TNM 8th edition for organ - confined prostate cancer. Pathologic sub - staging did not convey prognostic information either considering laterality as total tumor extent or index tumor extent. There were no significant clinicopathologic differences

by laterality considering either total tumor extent or index tumor extent, and no significant difference for time to biochemical recurrence using Kaplan - Meier product limit analysis as well as prediction of shorter time using Cox stepwise logistic regression.

ABBREVIATIONS

PSA = Prostate specific antigen
RP = Radical prostatectomy
BCR = Biochemical recurrence
TBCR = Time to BCR
DRE = Digital rectal examination

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Salvage radiotherapy for biochemical recurrence after radical prostatectomy: does the outcome depend on the prostate cancer characteristics?

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ABSTRACT

Objective: To build a model to evaluate the impact of salvage radiotherapy (SRT) in men with PSA rise or persistent PSA after undergoing radical prostatectomy (RP).
Materials and Methods: The study included 107 node-negative patients treated with SRT after RP at a single institution. Patients received SRT for either prostate-specific antigen (PSA) rising, or PSA persistence after RP. All patients received local radiation to the prostate / seminal vesicle bed. The primary measured outcome was the biochemical recurrence (BCR) free survival. Multivariable Cox regression analysis was used to develop a risk-stratification group to identify predictive factors associated with the probability of BCR at 5yr.
Results: At a median follow-up of 52 months, the BCR free survival rate and overall survival in 5 years was 73% and 94%, respectively. At multivariable analysis, pre-SRT PSA level > 0.35ng / mL (p = 0.023), negative margins (p = 0.038), and seminal vesicles invasion (p = 0.001) were significantly associated with BCR free survival. Three risk groups using regression analysis for SRT administration was built. Low-, intermediate- and the high-risk groups had a BCR free survival in 5-years of 96%, 84%, and 44% (p = 0.0001), respectively.
Conclusions: We developed a risk group stratification to show the impact of SRT based on prostate cancer characteristics. SRT showed to be extremely beneficial for patients with low- and intermediate-risk tumors. Moreover, the risk-group built could identify patients classified as high-risk who might benefit from more aggressive treatment for SRT.

ARTICLE INFO

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Radiotherapy; Prostatectomy; Prostatic Neoplasms

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INTRODUCTION

The treatment of biochemical recurrence (BCR) after radical prostatectomy (RP) is a clinically significant issue for radiation oncologists. It is estimated that about 30% of patients undergoing RP develop an increase in prostate-specific antigen (PSA) after radical surgery (1). Among the available treatment options for BCR after RP, salvage radiation therapy (SRT) is considered one of the most common treatment options employed in clinical practice. Although its use is recommended, its effectiveness has been found to be profoundly dependent on the PSA level at the time of treatment (2, 3). Despite the absence of randomized controlled data, many retrospective studies have shown that early SRT (SRT) was associated with improved BCR-free survival, metastasis-free survival, and cancer-specific survival (4, 5). Based

on these findings, eSRT is indicated specifically at a PSA level < 0.5ng / mL (2, 3).

Notwithstanding, the potential benefit of SRT must be weighed against the potential deleterious effect on functional outcomes, particularly, erectile function and urinary continence (6). Additionally, a considerable proportion of patients treated with post-surgery radiotherapy may experience early and late high-grade toxicity (7). BCR after RP has a natural history very well described and established, which does not often translate into clinical progression followed by cancer-related death (5, 8-10). However, the question if there are specific categories of patients in whom the effectiveness of SRT is superior or not to others remains open (11).

Consequently, patients with BCR and an indolent natural history may be overtreated with eSRT. In the opposite, ideal candidates for SRT may have the SRT postponed until the presence of occult metastatic disease at the time of PSA rise. Based on these concepts, we hypothesized that the impact of SRT on the biochemical control varies according to the clinical and pathological features of patients. Therefore, this study intended to build a model to evaluate the impact of SRT based on the clinical and pathological characteristics of men with PSA rise or persistent undergoing radical prostatectomy.

MATERIALS AND METHODS

One hundred and seven patients treated with SRT at one tertiary referral center between 2009 and 2015 were identified. The inclusion criteria were: patients undergoing RP with histologically confirmed ≥ pT2 tumor and submitted to pelvic lymphadenectomy (limited or extended) with pN0 adenocarcinoma of the prostate. The extension of pelvic lymphadenectomy varied according to the initial patient's risk group. All patients should have a Karnofsky performance status (KPS) > 70. Patients submitted to pelvic radiotherapy or combined treatment with androgen blockage were excluded from this cohort.

SRT was delivered for either PSA rising or PSA persistence after RP. PSA persistence was determined as a serum concentration ≥ 0.1ng / mL at one month after RP (2). SRT was delivered to the prostate and seminal vesicle bed. The clinical target volume (CTV) was drawn on computed tomography images. The CTV included the prostatic bed, periprostatic tissue, and the seminal vesicle bed. Clinical findings, pre-surgery computed tomography scan, and surgical clips guided the clinicians for the CTV definition. The planned target volume (PTV) was determined as CTV plus a 0.7-1.0cm margin due to the organ motion and the setup error. All patients were treated with high-energy photon beams (6mV) with a conventional fractionation (1.8-2Gy / fraction). Both techniques (three-dimensional conformal (3D-RT) and intensity-modulated radiation therapy (IMRT)) were used during the study period. The following clinical and pathological data were collected: age, preoperative risk group, preoperative PSA level, postoperative PSA level, the time between RP and PSA failure, pre-SRT PSA level, SRT dose, treatment technique, pathologic stage, pathologic Gleason score, surgical margin status, seminal vesicle invasion and extracapsular extension. The primary endpoint of this cohort was the biochemical failure after SRT. BCR after SRT was considered as the first PSA measure > 0.2ng / dL. Overall survival was established as death from any cause. Follow-up time was defined as the time between SRT and the BCR or last follow-up. Time zero was set at the time of SRT.

The secondary outcome of the study consisted of acute and late genitourinary (GU) and gastrointestinal (GI) toxicity, graded according to the Radiation Therapy Oncology Group and European Organization for Research and Treatment of Cancer criteria.

Statistical analysis

Statistical analysis was performed in three steps. In the first step, recognized predictive factors related with BCR found in the literature were tested in a univariate analysis using log-rank test. Variables with a p-value < 0.05 were selected to the next step. The second statistical step consisted of the Cox multivariate regression analysis with a bootstrapping correction. Bootstrapping is a method for obtaining robust estimates of standard

errors and confidence intervals for estimates such as regression coefficient. Bootstrapping was adjusted to resample in 1000 samples. This statistical technique is most useful as an alternative to parametric estimates when the assumptions of those methods are in doubt as in the case of regression models with small subgroup samples. Variables with p with $p < 0.05$ in the Cox regression model with bootstrapping were led to the third step. The third step consisted of the building of a risk group for SRT and BCR free survival. The risk group was classified as low-, intermediate- and high -risk groups according to the presence of significant factors identified in the multivariate analysis. This group was tested for BCR free survival rate using the Kaplan Meier and log-rank test, with a p-value < 0.05 considered significant. SPSS version 23.0 was used to perform all statistical analysis.

RESULTS

Descriptive characteristics of patients included in this cohort are described in Table-1. Overall, 78 (73%) patients received SRT for a rising PSA, whereas 29 (27%) received SRT for PSA persistence. The median SRT dose was 70Gy (IQR; 66, 70). IMRT was used in 66% of patients and 3D RT in 34%. Time between surgery and PSA recurrence was 14 months (IQR: 7, 39). The median pre-PSA level at SRT was 0.32 (IQR: 0.23, 0.52) ng / mL. The median follow-up time from SRT was 52 months (IQR: 36, 72); during follow-up, 26 patients had a BCR after SRT and 6 deaths were observed. In 5-years, the BCR rate after SRT was 73% (Figure-1a). Univariate analysis identified six variables associated with BCR. These variables were negative margin ($p = 0.003$), extracapsular extension ($p = 0.003$), preoperative risk group ($p = 0.005$), seminal vesicle invasion ($p = 0.001$), PSA level > 0.35ng / mL ($p = 0.010$) at SRT, and SRT dose < 70Gy ($p = 0.018$) (Table-2). The Cox regression identified PSA > 0.35ng / dL ($p = 0.023$), negative margins ($p = 0.038$), and seminal vesicles invasion ($p = 0.001$) as independent factors related to a poor BCR free survival (Table-3).

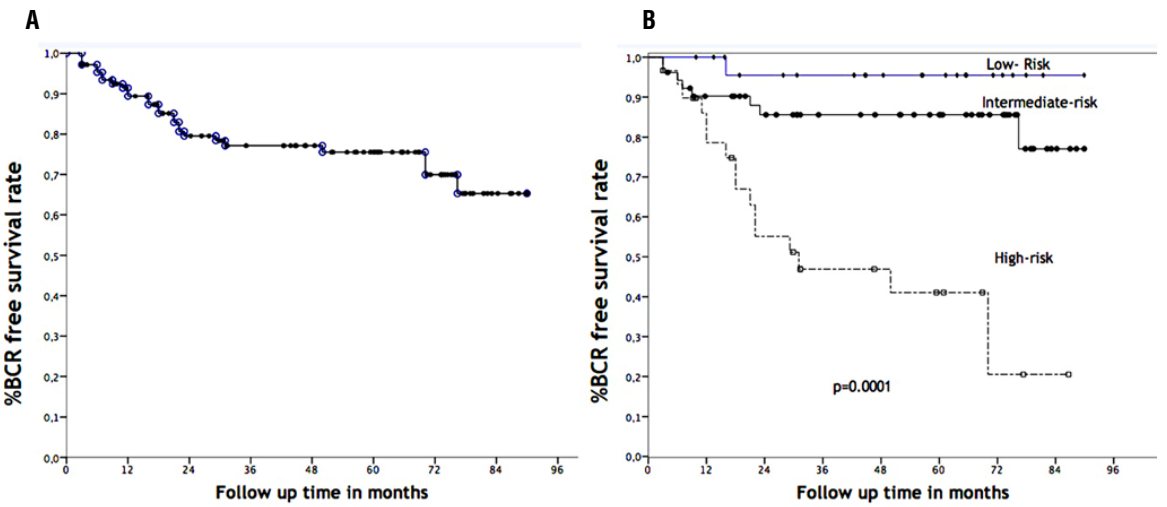
A risk-group was built using the independent factors identified in Cox regression. Patients with no risk factors identified in Cox regression

Table-1 - Descriptive characteristics of 107 patients undergoing radical prostatectomy (RP) with rising PSA after surgery and submitted to salvage radiotherapy (SRT).

Variables	Median (IQR)
Age at SRT	70 (64 - 75)
Pre operative PSA ng/mL	9 (6 - 13)
Pathological stage	
pT2a-c	41(38.3%)
pT3a	39(36.4%)
pT3b	27(25.3%)
Pathological Gleason score	
≤ 6	20 (18.7%)
7	74 (69.2%)
8-10	13 (12.1%)
Postoperative PSA persistence	
No	78(72.9%)
Yes	29(27.1%)
Risk group pre-surgery	
Low	13(10.5%)
Medium	46(43.8%)
High	48(45.7%)
Surgical margin status	
Positive	80(74.7%)
Negative	27(25.3%)
Time between RP and SRT (mo)	14 (7-39)
PSA at SRT (ng/mL)	0.32 (0.23 - 0.52)
RT technique	
3D-RT	71(66.4%)
IMRT	35(32.7%)
SRT dose (Gy)	70 (66 - 70)
Follow up time after SRT (mo)	52 (36 - 71)
Follow up time after RP (mo)	

IQR = interquartile; mo = months, **Gy =** gray; SRT = salvage radiotherapy; **RP =** radical prostatectomy; **3D-RT =** conformational radiotherapy; **IMRT =** intensity modulated radiotherapy.

Figure 1 - Biochemical recurrence free survival for the entire cohort (a) and biochemical recurrence for the risk groups (b).



analysis were classified as low-risk, and the BCR after SRT in 5-years was 96%; while patients with one risk factor were classified as intermediate - risk and had 84% of BCR rate in 5-years and patients with two or more independent factors had 44% of BCR after SRT, p = 0.0001 (Figure-1b).

The acute GU and GI toxicity grade 2 or higher according to the RTOG criteria was 2.8% and 0, whereas the rate of late GU and GI toxicity grade 2 or higher were 11% (7.8% grade 2 and 3.7% grade 3) and 0, respectively (Table-4).

DISCUSSION

The present cohort study hypothesized that SRT has a distinct effect on cancer control depending on clinical and pathological features. Our results validated this hypothesis, once we identified three prognostic risk groups of patients in which SRT had a different outcome.

Our findings agree with other series, which reported several of the factors associated with BCR and SRT (4, 5, 12-15) (Table-5). However, in the present analysis, we classified patients according to their clinical and pathological features. Using this strategy, we build a prognostic risk--group with significant different BCR according to their classification (Figure-1b). Indeed, we observed a significant impact of SRT in low-, and intermediate-risks, whereas the outcome of SRT did not result in a satisfactory BCR free survival rate for high-risk patients. Especially, low-risk patients had a considerably favorable 5-yr BCR of 96%. In the opposite, high-risk patients did not achieve an entirely favorable 5-yr BCR rate of 44%, suggesting that these patients need more aggressive treatment such as pelvic radiation and / or combined treatment with androgen blockage.

In this scenario, to investigate a more aggressive approach for patients with BCR after radical prostatectomy, the GETUG-AFU 16 randomized 743 men with a BCR after radical prostatectomy (PSA > 0.1ng / mL). The arms of randomization were salvage RT with a six-month course of ADT (goserelin) or to salvage RT alone.

The combined treatment significantly prolonged the five-year progression-free survival compared with RT alone (80 vs. 62%), but with no improvement for overall survival (96 vs. 95%) (16). Another trial conducted by the RTOG group (RTOG 9601) randomized 760 men with a detectable PSA (0.2 to 4.0ng / mL) following radical prostatectomy to RT and placebo or RT with antiandrogen therapy for 24 months (bicalutamide 150mg / day). Overall survival at 12 years was 76 percent in the bicalutamide group and 71 percent in the placebo group. Prostate cancer mortality at 12 years was reduced to 8% in the bicalutamide group (p < 0.001). The

Table-2 - Univariate analysis of factors related with biochemical recurrence (BCR) after salvage radiotherapy (SRT).

Variables	% BF control in 5 years	P Value
Age at SRT		0.303
< 70 years	82%	
≥ 70 years	67%	
Gleason		0.125
≤ 7	90%	
> 7	72%	
Extracapsular extention		0.003
Yes	85%	
No	66%	
Seminal vesicles involvement		0.001
Yes	85%	
No	59%	
Postoperative PSA persistence		0.967
Yes	72%	
No	77%	
Risk group pre surgery		0.005
Low	100	
Medium	80	
High	66	
Surgical margin status		0.003
Positive	88%	
Negative	66%	
Time between RP and SRT (mo)		0.623
< 24 months	72%	
≥ 24 months	77%	
PSA at SRT		0.01
PSA < 0.35	86%	
PSA > 0.35	62%	
RT technique		0.393
3D-RT	74%	
IMRT	76%	
SRT dose		0.018
< 70 Gy	65%	
≥ 70 Gy	79%	

Table-3 - Cox regression analysis with bootstrapping resample for predictive factors associated with BCR after SRT.

Predictor	HR	CI95%	P value
Seminal Vesicles status			0.001
Negative	1	Ref	
Positive	4.5	1.9-10.7	
Surgical margin status			0.038
Positive	1	Ref	
Negative	2.6	1.06- 6	
PSA at SRT			0.023
PSA < 0.35	1	Ref	
PSA ≥ 0.35	2.76	1.15-6.6	

Table-4 - Maximal acute and late gastrointestinal (GI) and genitourinary toxicity according to RTOG criteria.

Grade	Acute GU	Acute GI	Late GU	Late GI
0	64 (59.8%)	93 (86.9%)	57 (53.2%)	101 (94.4%)
1	40 (37.4%)	14 (13.1%)	38 (35.5%)	6 (5.6%)
2	3 (2.8%)	0	8 (7.4%)	0
3	0	0	4 (3.7%)	0
4	0	0	0	0

Table-5 - Outcomes with salvage radiotherapy (SRT) from contemporary retrospectives studies in prostate cancer patients undergoing radical prostatectomy (RP) and PSA rise.

Author	N	PSA at SRT	RT technique	RT dose	Follow-up	BCR	Predictors response
Moreira et al. (12)	102	0.6 ng/mL	NA	66 Gy	50 mo	6yr:57 %	Surgical margins Pre-SRT PSA levels
Umezawa et al. (13)	102	0.24 ng/mL	NA	64 Gy	44 mo	4yr; 51%	Pathologic stage
Parekh et al. (14)	108	0.24 ng/mL	NA	66.4 Gy	63 mo	4yr; 45%	Pre-SRT PSA levels ADT
Lohm et al. (15)	151	0.34 ng/mL	3D-RT	66.6.Gy	82 mo	5yr: 40%	Pre- SRT PSA levels Gleason score PSADT
Present study	107	0.32 ng/mL	3D-RT/IMRT	70 Gy	53 mo	5yr: 73%	Negative margins Pathological stage Pre- SRT PSA levels

beneficial effect of bicalutamide was most evident in patients with a pre-RT PSA of ≥ 0.7ng / mL. These data from randomized clinical trials show that prostate cancer with unfavorable risk factors needs more multimodal treatments (17).

On the other hand, our risk group contests the current conviction of indication of SRT using only the PSA level for driving the decision for all patients independent of disease features. Consequently, it is possible to postpone SRT in selected patients with no compromise of the oncologic outcome. Thus, our findings revealed a clear benefit of SRT in distinct subgroups of men with either BCR or PSA persistence after RP. Other previous studies have also discussed the real necessity and when administering SRT (1, 4, 5). Notwithstanding, contrasting results have been published and the question remains unanswered. Currently, three ongoing randomized clinical trials are investigating the role of early salvage radiotherapy compared with adjuvant radiotherapy in patients with unfavorable pathological features (18-20). Adjuvant RDT is well established. These trials will try to answer questions like: how to improve the selection and avoid overtreatment for patients with PSA rising? What is the best timing to SRT?

Unfortunately, due to our sample size, we could not study the interaction among the predictive variables in this cohort. However, in a recent publication, Fossati and colleagues studied 925 patients treated by SRT due to a PSA recurrence after RP in seven institutions. In their findings, a significant relationship between cancer control with SRT and PSA level was observed (21). The chance of controlling the disease was remarkably small with a PSA level higher than 1ng / mL. Thus, SRT should be delivered at the first sign of PSA rising. Although, our analysis is completely differentiated from Fossati et al. (21), our data has the same direction of them, once the pre-PSA level at SRT < 0.35ng / mL was a strong predictor for BCR free survival. A meta-analysis evaluating the relationship between the PSA level at SRT and BCR rate also reinforced our findings. In this study, more than 5.500 patients were treated with SRT. The authors observed a 2.6% loss of BCR-free survival for each incremental of 0.1ng / mL in the PSA level at the time of SRT (22). Furthermore, a recent tumor control probability model observed that the deleterious effect of increased PSA levels at the time of SRT could never be counterbalanced by increasing the SRT (23). Consequently, international guidelines suggest delivering SRT at the first sign of BCR. However, which is the best moment for SRT administration is still debated. Our data shows that the pre-PSA level is the driver to guide the decision of indicating SRT, but other predictive factors as margin and vesicles status can help to guide the decision; mainly, when these both factors are present, SRT should be administered at low PSA level. Looking at the characteristics of our risk groups, although the interval time between RP and SRT was shorter for the high-risk group than low-risk group, the PSA level at SRT was also higher in the high-risk group. This data calls attention for the kinetics of PSA, genetic differences among the prostate cancer cells and the use of refined imaging tests like PSMA-PET during the close follow-up to select adequate treatment volume and dose to SRT at a lower PSA level for these patients.

The relationship between RT total dose and biochemical control is well known in prostate cancer patients with intact prostate gland treated with radiotherapy. This relationship has led some authors to test the hypothesis that higher doses might be beneficial even in men undergoing SRT (24). However, the clinical guidelines often suggest that at least a dose of 64-65Gy should be given (3). In our study, a dose of 70Gy was associated with a better BCR than lower doses. This finding is also in agreement with other authors. For instance, Stish et al. (25) identified that SRT with a dose of 68Gy or greater significantly reduced the risk of BCR in a large contemporary cohort. Two meta-analyses also studied this question. In these studies, a 2-2.5% improvement in recurrence-free survival for each additional Gy delivered was noted (22, 26).

Regarding late toxicity, analyzes of multiple series have found approximately 15% rates of RTOG grade 2 GI toxicity and < 5% rates of grade 3 toxicity (27). Rates of grade 2 and 3GU toxicity are reported to be approximately 10% grade 2 and 5% grade 3 in both multi- and single-institution studies (28, 29). In our study to date, the reported rate of Grade 2 late

GU was 8%, with 3.7% of grade 3, and with no cases of grade 2 or 3 late GI toxicity.

Finally, this cohort has inherent limitations as a retrospective, single-institution analysis, which is similar to other observational studies. However, we tried to limit other sources of biases using a strict selection criterion to evaluate the impact of SRT in different risk groups. We decided to include only patients treated with SRT delivered to the prostate bed with no pelvic radiation or combined treatment. However, even selecting an ideal sample to build a risk group stratification for SRT, we could not examine the role of PSA kinetic and neither prostate cancer-specific survival due to 5 years follow-up. Also, we could not evaluate the role of genetic arrays or use recent refined imaging tests like PSMA-PET to select or stratify more adequately patients into different risk groups for SRT.

CONCLUSIONS

The present study confirms the satisfactory disease control with SRT in patients with PSA rise after RP. Our data also reinforce the role of several predictive factors related to the biochemical failure in that scenario. Based on the predictive factors, we could build a risk group classification to assess the risk of BCR after SRT for PSA rise after RP.

Three different risk groups were recognized based on clinical and pathologic characteristics. The risk group classification had a satisfying performance adequately distinguishing patients with distinct outcomes. The low- and intermediate risk patients had an excellent and satisfactory result with SRT, respectively. Conversely, for the high-risk patients, SRT had a poor outcome.

These findings can be useful to identify the optimal candidates for SRT and reinforce the importance of the PSA level at the time of SRT, mainly, in the presence of other significant predictive factors. External validation of these data in a large sample combined with other refined tools such as genetic arrays and PSMA-PET is necessary to help improve the cancer control while avoiding overtreatment or undertreatment.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Can expressed prostatic secretions affect prostate biopsy decision of urologist?

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ABSTRACT

Objectives: To evaluate the frequency of NIH category IV prostatitis, and the use of expressed prostatic secretions tests in an effort to improve the reliability of prostate specific antigen as an indicator, to avoid unnecessary prostate biopsy.
Materials and Methods: 178 expressed prostatic secretion positive patients with serum prostate specific antigen levels of ≥ 2.5 ng / mL were included in present prospective study. The diagnostic evaluation included detailed history and physical examination, digital rectal examination, urine analysis, urine culture, and expressed prostatic secretions tests. Transrectal ultrasonography was used both to measure prostate volume and conduct 12 core prostate biopsy.
Results: The prevalence of NIH category IV prostatitis was 36.9% (178 / 482) in our population of men. In our study patients (n: 178) prostate biopsy results were classified as; 66 prostatitis, 81 BPH, and 31 Pca. In asymptomatic prostatitis group, expressed prostatic secretion mean leucocyte ratio was higher compared to other two groups ($p < 0.0001$). The relation between number of expressed prostatic secretion leucocytes and prostatitis, benign prostate hyperplasia, and prostate cancer is analyzed. If 16 is taken as the cut of number for leucocyte presence, its sensitivity is 0.92 (AUC = 0.78 $p = 0.01$).
Conclusions: The number of leucocytes in expressed prostatic secretion is higher in the chronic prostatitis group. If the leukocyte presence of 16 and above is taken as the cut off point, the sensitivity becomes 0.92 (AUC = 0.78). We firmly believe that our new cut off value may be used as to aid prostate specific antigen and derivates while giving biopsy decision.

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INTRODUCTION

In 1979 Wang et al. discovered Prostate Specific Antigen (PSA) (1). This antigen is secreted from the prostate ductal epithelial cells. PSA has become an important tool in Prostate cancer (Pca) screening and the incidence of Pca patients increased with the introduction of PSA into the clinical practice (1). PSA is organ specific but not cancer specific. However, increased PSA levels are also associated with conditions other than cancer, such as benign prostate hyperplasia (BPH), prostatitis and non-malignant conditions. These conditions can cause an increase in serum PSA levels that lead to potentially unnecessary biopsy procedures, increasing inconvenience for the patient, and cau-

sing over-diagnosis, over-treatment and elevated medical costs (2). Pca is determined in only 38% of biopsies performed on the basis of PSA elevation (3).

National Institute of Health (NIH) classified prostatitis into 4 categories in 1995. NIH defined Category IV as asymptomatic chronic prostatitis due to the presence of inflammatory cells either in expressed prostate secretions (EPS) or during histopathological examination of prostatic biopsies from asymptomatic men (4).

Empiric use of antibiotics in an asymptomatic patient in order to lower the PSA is common in current clinical practice. Previous studies examining this subject have yielded conflicting results. While some studies state that serum PSA can be reduced with a course of antibiotics (5, 6), other studies state that treating patients with antibiotics does not lower serum PSA levels (7-9). Some guidelines mentioned that "However, antimicrobial therapy for selected patients with category IV prostatitis associated with elevated PSA, infertility and those planned for prostate biopsy may warrant consideration (3: C)" (10). Generally in these studies, not only EPS positive patients, all clinically asymptomatic men with elevated PSA levels have evaluated.

There are several implications in the use of empiric antibitics for patients with elevated PSA levels such as cost and toxicity. In addition, there is concern that the indiscriminate use of empiric antibiotics could lead to the development of resistant bacterial species and thereby expose the patient to more resistant and aggressive sepsis.

Despite extensive research efforts, very few biomarkers of prostate cancer have been successfully implemented into clinical practice today and the PSA test is still the most important biomarker for the detection and follow-up of prostate cancer. Numerous studies of serum (PSA isoforms, prostate health index and other combinations), tissue (p63, AMACR, PSMA, Glutathione S-transferase P, etc.) and urine based (PCA 3, SPINK 1, Annexin A3, etc.) prostate cancer biomarker candidates have been presented during the last ten years (11-15). These biomarkers seem to be promising. Some of them is already in current daily practice and highly satisfactory results are being reported. However, these are not widely used because of cost, accessibility, their experimental manner or complexity of usage.

The aim of this prospective study was to further investigate the predictive role of the number of leukocytes in expressed prostate secretions in differentiating histological inflammation from PCa and other non neoplastic lesions. Also, to evaluate the use of EPS tests in an effort to improve the reliability of PSA as an indicator, to avoid unnecessary prostate biopsy.

MATERIALS AND METHODS

After institutional review board (ethical committee) approval, all study participants provided informed written consent before enrolment and 482 men were recruited in the present prospective study. Patients underwent a four-specimen study according to Meares-Stamey method (16). After periurethral cleaning with alcohol sponge, the patient provided a VB 1 specimen consisting of the initial 5 to 10 mL of voided urine, followed by a VB 2 specimen. Patients were placed in a lithotomy position, and a physician wore liquid parafin-coated gloves to perform digital rectal examination and several bilateral and middle prostatic massages. After production of EPS by digital prostatic massage, the patient provided 5 to 10 mL of voided urine for the VB3 specimen. EPS was positive in 178 of 482 patients. Eligibility criteria included referral for initial PSA between 2.5 ng / mL and 20.0 ng / mL, EPS positivity and palpably normal digital rectal examination. Exclusion criteria were; 1) pyuria (more than 3 leukocytes), 2) urinary tract infection history 3) urethral disorder history, 4) 5 alpha reductase treatment 5) antibiotics or anti-inflammatory therapy within last 2 months, 6) neurological disorders with an impact on lower urinary tract function, 7) urethral stricture, 8) former prostate biopsies or genitourinary surgery, 9) urological intervention within last month, 10) presence of acute urinary retention, 11) permanent urethral catheter, and 12) former prostatitis diagnosis and antibiotic therapy history. After a detailed physical examina-

tion, a digital rectal examination was made. Urine analysis, urine culture, anti-biogram and EPS tests were done for all participants. Prostate fluid samples following prostate massage were obtained from all patients. The liquid samples were counted for leukocytes on microscope slides with a large enhancement (40 X), if the number of leukocytes was ≥ 10, it was considered as positive for prostate inflammation. Prostate volume measurements were made and Ultrasound-guided 12 core prostate biopsy was taken using 18 G 30 cm needle automatic prostate biopsy gun. Biopsy results were classified as BPH, NIH category IV prostatitis and Pca. If Pca and prostatitis observed together in biopsy pathology, it was classified in Pca group. If ≤ 3 of 12 core had evidence of prostatitis, it was classified in BPH group. If ≥ 4 of 12 core had evidence of prostatitis, it was classified in prostatitis group. Prostat volumes were measured using 0.5 (LxWxH) formula (L: length from top to bottom W: horizontal length H: anterior posterior length). Data analysis was made using SPSS 15.0 Software Package Program (descriptive statistical analysis, ANOVA post hoc test, correlation test, Roc curve).

RESULTS

The prevalence of NIH category IV prostatitis was 36.9% (178 / 482) in our population of men. In our study patients (n: 178) prostate biopsy results were classified as; 66 prostatitis, 81 BPH, and 31 Pca (Table-1). None of the patients, diagnosed with prostatitis in histopathological analysis had symptomatic or asymptomatic prostatitis history or former antibiotics therapy due to prostatitis. There was no statistically significant difference between prostatitis, BPH, and Pca groups in terms of age ($p = 0.37$). Likewise no statistically significant difference was seen among the three groups in terms of prostate volume ($p = 0.40$). A statistically significant relation and a strong correlation between tPSA level and prostate volume was present ($p < 0.05$ $r = 0.68$).

When prostatitis, BPH, and Pca groups were evaluated according to tPSA levels, there was a statistically significant difference between BPH and Pca ($p = 0.022$). In terms of tPSA, there was no statistically significant difference between the BPH-prostatitis ($p = 0.21$) groups and Pca-prostatitis groups ($p = 0.45$) ($p > 0.5$). In terms of free PSA (fPSA), no statistically significant difference was seen between in the BPH-Prostatitis group ($p = 0.99$), and in BPH-Pca ($p = 0.72$), or Prostatitis--Pca ($p = 0.84$) groups.

In the prostatitis group the number of leukocytes in the EPS was higher than in the other two groups ($p < 0.0001$). The relation between the number of leukocytes in the EPS and prostatitis, BPH, and Pca was also evaluated. The most appropriate cut off value for the amount of leucocytes in the prostate massage fluid was determined as ≥ 395 (in a high enhancement area with a mean of

Table 1 - General features of the Patients and Distribution.

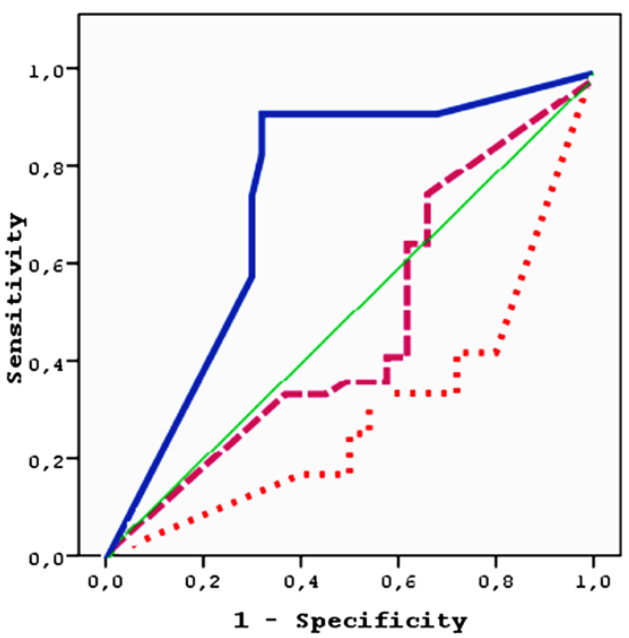
	Asymptomatic prostatitis	BPH	Prostate Ca	p
Age	54.50 ± 7.8	62.8 ± 8.8	64.3 ± 9.4	0.37
Total PSA (ng/mL)	8.31 ± 16.4	7.38 ± 3.9*	10.4 ± 8.5*	0.022*
Free PSA (ng/mL)	1.26 ± 1.13	1.15 ± 0.61	1.16 ± 0.50	>0,05
fPSA/tPSA	0.16±0.09	0.21±0.14+	0.11±0.09+	0.001+
Prostate vol. (mL)	40.38 ±29.4	41.6 ± 20.9	37.1 ± 21.7	0.40
EPS	26.7±9.7&	13.8±13.9	11.3 ± 14.2	<0.0001&

mean±SD

* Difference between PCa and BPH; + Difference between Pca and BPH; & Difference prostatitis with Pca and BPH

≥ 16) as shown in Figure-1. In the Roc curves drawn, statistical significance was only determined in the area under the curve between the number of leukocytes with prostatitis (AUC = 0.78 p = 0.01 prostatitis sensitivity: 0.92).

Figure 1 - Number of Leukocytes in Prostate Massage Fluids; Prostatitis, BPH, and Pca Relations (Straight line: prostatitis, Dashed line: BPH, Dots: Pca).



DISCUSSION

The incidence of Pca patients who diagnosed at low stage, increased because of widespread using PSA testing. The rate of detecting Pca clinically in elevated levels of serum PSA ranges between 17.5% and 38% (3). PSA estimated sensitivity at the cutoff 4.0 ng / mL value is 21% for detecting any prostate cancer and specificity is 91% (17). There is however, a wide range (10-80%) of reported false positivity (18, 19). Determining the accuracy of PSA testing is confounded by the fact that most men with normal PSA values do not undergo biopsy, overestimating sensitivity and underestimating specificity.

Chronic prostatitis is a disease still without a clear etiology. Polymorphonuclear leukocyte invasion is determined in the intra-prostatic channels and peri-prostatic tissue during histopathological analyses (20, 21). Chronic prostatitis may present itself with very different clinical presentations. According to their clinical and laboratory findings, NIH classified prostatitis into 4 categories in 1995.

Various studies about the prevalence of prostatitis subtypes determined by NIH have been conducted. In studies made with needle biopsy analyses, prostatitis incidence ranging on a large scale between 17.2% and 42% have been reported (22, 23). However, studies on prevalence of NIH category IV prostatitis are very scarce. In a study made on a prostate cancer awareness screening program population, NIH category IV prostatitis incidence was determined as 32.2% (24). In the present study a rate of 36.9% was determined.

PSA, an important tumor marker, is organ but not cancer specific, studies about new methods verifying PSA results are in progress. To reduce unnecessary biopsies and to improve on PSA specificity, past research primarily investigated PSA derivatives. These have included PSA velocity, PSA density, age-specific PSA, fractionated PSA and percentage of free prostate-specific antigen (% fPSA) (25). Forexample; % fPSA is of some diagnostic use, although without significantly reducing the rate of negative biopsies. In particular, in a recent study, % fPSA has been documented as a poor discriminator between chronic prostatitis and Pca (11).

Urologists often manage asymptomatic men with a high serum PSA level by observation after antibiotic treatment. Because inflammation can often result in elevated PSA at documented chronic bacterial prostatitis patients. But studies examining this subject in the asymptomatic population have yielded conflicting results. While some studies state that serum PSA can be reduced with a course of antibiotics (5, 6), other studies state that treating patients with antibiotics does not lower serum PSA levels (7-9). Recently, in a prospective, controlled study by Greiman et al., 136 asymptomatic men with elevated PSA were divided into a ciprofloxacin treatment group (n = 63) or observation group (n = 73) where the study group received six weeks of ciprofloxacin and the

observation group did not receive treatment (26). They continued routine follow-up for an average of 4.6 years with routine PSA, exam and prostate needle biopsy per clinical practice guidelines. The primary endpoint of this study was change in serum PSA, while the secondary endpoint was presence or absence of prostate cancer on biopsy. This study found a borderline statistically significant change in serum PSA between patients randomized to a 6-week course of fluoroquinolones versus observation, and no difference in positive prostate biopsy results. The authors suggest that patients with an elevated serum PSA could not treated with antibiotics in the absence of clinical symptoms of prostatitis. The literature does not support the evidence that antibiotics alter PSA levels except in the presence of bacterial prostatitis. Also, Heldwein et al. showed that PSA levels tend to fall when repeated after 45 days, regardless of antibiotic treatment (27).

Prostatitis should be diagnosed if there are 10 and more leukocytes present in a high enhancement area (40 X). According to the findings of the present study, number of polymorphous nuclear leucocytes in prostatitis group is higher than in BPH and Pca groups ($p < 0.0001$). Normally, 10 or more leucocyte counts are sufficient for prostatitis diagnosis. However, the number of leukocytes at the prostate massage fluid in the prostatitis group was higher than the other two groups, so that have us an idea.

We thought that, if a new cut off value for leucocyte presence in prostatic fluid is determined, the predictability of prostatitis will be increased and thus unnecessary biopsies may be avoided. The outcome of the Roc curve analysis revealed that average leucocyte presence of ≥ 16 or total leucocyte presence of ≥ 395 is most appropriate and should be taken as the new cut off point in a large enhancement area. The analyses revealed AUC = 0.78 and sensitivity for prostatitis as 0.92.

In summary, if the number of leucocytes is 16 and above in the prostatic massage fluid, this may most probably an indicator of prostatitis driven PSA increase. Previous to a biopsy decision, this new cut off value may be applied in clinical practice when encountering a asymptomatic patient presenting for the first time with an elevated PSA and without clinical evidence of prostatitis. Also, we recommend in these patients, it may be more beneficial to utilize other tools such as PSA velocity, PSA density, complexed PSA or newer clinical tools such as the prostate health index. Our new cut off value may be used to lend assistance these tools before biopsy decision.

Our study has some methodologic factors that might affect accuracy of our estimates. We didn't correlate the EPS results with histology results of our biopsy. Because, we classified chronic inflammation histologically as; available or unavailable. We didn't make detailed classification. Chronic inflammation of the prostate was defined as infiltration of prostate biopsy specimens by inflammatory cells, lymphocytes, plasma cells and / or histiocytes. Irani et al. classified inflammation with regard to the histological grade and aggressiveness of the inflammatory process: histological grades 0 and 1 were regarded as the "non-inflammation group", and histological grades 2 and 3 as the "inflammation group" (28). This classification system is more objective for the correlation of EPS results with histology results. Engelhardt et al. used this classification for to evaluate the possible correlations between chronic asymptomatic inflammation of the prostate type IV and prostate cancer in patients undergoing radical prostatectomy (29). In another study, it was used for to investigate the association of the expression of tumor necrosis factor-α (TNF-α) with asymptomatic inflammatory prostatitis National Institutes of Health (NIH) category IV and prostatic calculi, in patients with obstructive benign prostatic hyperplasia (BPH) treated by transurethral electroresection of the prostate (TURP) (30).

CONCLUSIONS

The number of leucocytes in EPS is higher in the chronic prostatitis group. If the leukocyte presence of 16 and above is taken as the cut off point, the sensitivity becomes 0.92 (AUC = 0.78). We firmly believe that our new cut off value may be used as to aid PSA and derivates while giving biopsy decision. Further investigations will be necessary to evaluate our new cut-off value accuracy and determine exact cut-off points.

ABBREVIATIONS

PSA = Prostate Specific Antigen
Pca = Prostate cancer
BPH = Benign prostate hyperplasia
NIH = National Institute of Health
EPS = Expressed prostatic secretions
tPSA = Total PSA
fPSA = free PSA

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Safety and effectiveness evaluation of open reanastomosis for obliterative or recalcitrant anastomotic stricture after radical retropubic prostatectomy

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ABSTRACT

Purpose: To evaluate safety, efficacy and functional outcomes after open vesicourethral re - anastomosis using different approaches based on previous urinary continence.

Materials and Methods: Retrospective study of patients treated from 2002 to 2017 due to vesicourethral anastomosis stricture (VUAS) post radical prostatectomy (RP) who failed endoscopic treatment with at least 3 months of follow-up. Continent and incontinent patients post RP were assigned to abdominal (AA) or perineal approach (PA), respectively. Demographic and perioperative variables were registered. Follow-up was completed with clinical interview, uroflowmetry and cystoscopy every 4 months. Success was defined as asymptomatic patients with urethral lumen that allows a 14 French flexible cystoscope.

Results: Twenty patients underwent open re-anastomosis for VUAS after RP between 2002 and 2017. Mean age was 63.7 years (standard deviation 1.4) and median follow-up was 10 months (range 3 - 112). The approach distribution was PA 10 patients (50%) and AA 10 patients (50%). The mean surgery time and median hospital time were 246.2 ± 35.8 minutes and 4 days (range 2 - 10), respectively with no differences between approaches. No significant complication rate was found. Three patients in the AA group had gait disorder with favorable evolution and no sequels.

Estimated 2 years primary success rate was 80%. After primary procedures 89.9% remained stenosis - free. All PA patients remained incontinent, and 90% AA remained continent during follow-up.

Conclusion: Open vesicourethral re - anastomosis treatment is a reasonable treatment option for recurrent VUAS after RP. All patients with perineal approach remained incontinent while incontinence rate in abdominal approach was rather low.

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INTRODUCTION

Radical prostatectomy (RP) is a well - established procedure for the treatment of localized prostate cancer (1-4).

Most frequent long term complications mentioned are: sexual dysfunction, urinary incontinence and vesicourethral anastomosis stenosis (VUAS). The latter one, is a rare but troublesome complication with an incidence of approximately 8.4% (5-10). It's well known that the endoscopic approach provides good results; success rates vary from 50 to 91% with a mean of 2.1 interventions per patient (2, 11, 12).

Despite this, some patients show VUAS recurrence after endoscopic approach, in which case an open surgical reconstruction is the recommended procedure.

Open procedures can be addressed by different approaches: perineal, abdomino - perineal and abdominal (12-14). Perineal approach has the advantage of being an unspoiled surgical access, nevertheless, because of the urethral mobilization, this approach is associated with high rate of urinary incontinence (UI) (11, 15), thus, an artificial sphincter urinary (AUS) is mandatory. Some authors recommend that all patients must be counselled that this will almost certainly be a two - stage reconstruction, the first to clear the urethral obstruction by revision of the vesicourethral anastomosis and the second to implant an artificial sphincter for the almost inevitable sphincter weakness incontinence following this clearance (16).

Since the VUAS is proximal to the sphincter, some authors prefer the abdominal approach in order to preserve the external sphincter function and therefore the continence. Other advantage may be to keep the bulbar urethra intact in case there is a need for a subsequent AUS implantation.

This paper presents an update of our experience in open re-anastomosis for recurrent VUAS by either perineal or abdominal approach.

OBJECTIVES

To evaluate safety, efficacy and functional outcomes after open vesicourethral re - anastomosis (ORA) using different approaches based on previous urinary continence.

MATERIALS AND METHODS

Retrospective observational study. Data from patients treated for VUAS post radical prostatectomy in our hospital from 2002 to 2017 was retrospectively analyzed. The data collection was prospectively done from the electronic clinical history.

Patients with recalcitrant VUAS post RP (defined as the failure of more than three endoscopic treatments) and those with obliterated VUAS post RP were included in the analysis. Patient were included in this study only if they had at least 3 months of follow-up.

All patients underwent preoperative retrograde urethrography and voiding cystourethrography. Approach was chosen according to continence status before open reconstruction. We define as continent, after radical prostatectomy and subsequent endoscopic attempts for VUAS, as no need of any pads or only one. Incontinence was defined as the need of more than one pad. For continent patients, abdominal approach was chosen in order to preserve external sphincter. Perineal approach was offered to incontinent patients considering the benefit of an undamaged surgical field.

Variables registered were: surgical time, need for blood transfusion, intraoperative complications, hospital convalescent time, as well as postoperative complications related to the different approaches (complications were assessed using the Clavien - Dindo score), orthopedic complications / issues, and free rate re-stenosis and postoperative UI defined as the use of more than one pad per day.

Follow-up was carried out with clinical interview, uroflowmetry and cystoscopy every 4 months. Success was defined as asymptomatic patients with urethral lumen that allows a 14 French flexible cystoscope. Failure was defined as the need for any new treatment in order to restore the urethral lumen after ORA.

Continence after ORA was defined by the need of pads: one or none as continent and more than one as incontinent. Erectile dysfunction was defined as the patient's inability to achieve an erection that allows penetration.

For this study we inform the results of the last follow-up or those at the time of re - stenosis to avoid self - correlation bias.

SURGICAL PROCEDURES

Perineal approach: With the patient in a forced lithotomy position, lambda perineal incision was made, dissection of planes to reach the VUAS. Flexible cystoscopy (14 Fr) was done to confirm localization of the stenosis. Extensive

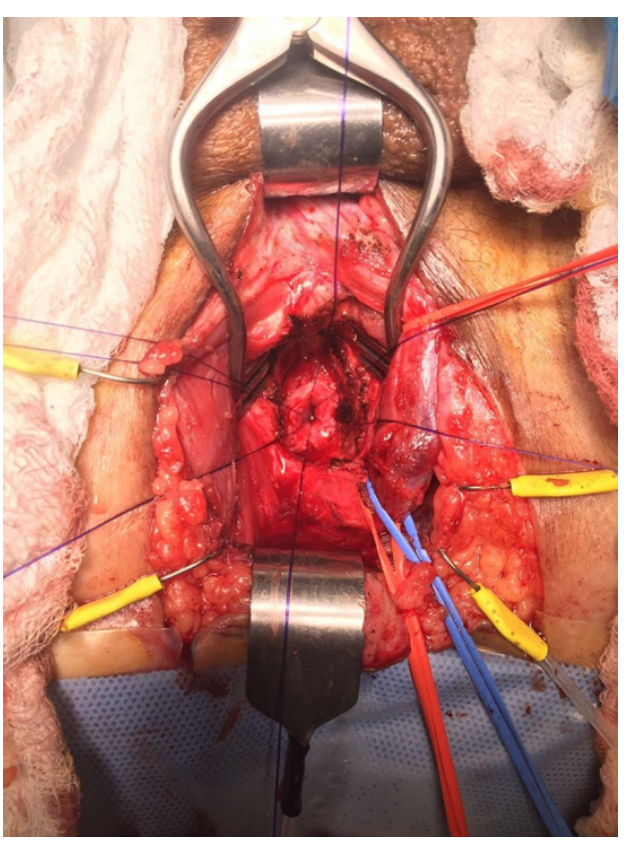
mobilization of the anterior urethra was performed. Opening of the crura and / or partial pubectomy was performed if needed. In patients with patent urethral lumen, an urethral catheter was introduced with cystoscopic aid. In cases with complete obliterated stenosis an abbocath® catheter was introduced into the bladder through the fibrotic tissue guided under cystoscopy by the suprapubic traject. With this maneuver we perform the anastomosis in the anatomical bladder neck spot.

Resection of the scarred tissue segment and vesicourethral re - anastomosis was constructed with six interrupted sutures of PDS 4 / 0. When possible, the corpus spongiosum was not transected (Figure-1).

Silastic 18 Fr urethral catheter was placed, which was removed under radioscopic control after 3 - 4 weeks (Figure-2).

Abdominal approach: The patient was placed in dorsal decubitus, infraumbilical medial incision was made, dissection of the pre - vesical area was performed. After complete mobilization of the bladder was achieved, partial pubectomy was performed to access the vesicourethral anastomosis site. The stenotic site was identified with a flexible cystoscope (14 Fr) and at the point of the stenosis, the bladder neck is divided. The fibrosis is removed and healthy bladder is dissected from the rectum. With benique® catheter through the urethra, placed in retrograde fashion, the urethra is dissected around the benique® and the fibrosis is completely removed. Urethral and bladder mobilization is necessary to achieve a tension free anastomosis. Then, we performed re - anastomosis with PDS 4 / 0 interrupted sutures (Figures 3 and 4). Silastic 18 Fr catheter and suprapubic cystostomy were placed. The urethral catheter was removed under radioscopic control after 3 - 4 weeks (Figure-5).

Figure 1 - Urethral lumen previous to re anastomosis by perineal approach. Note that the bulb was not transected so proximal irrigation is intact.



Statistical analysis: continuous variables with normal distribution are informed as their mean and standard deviation (sd). If there is non - parametric distribution, they are expressed by their median and range (r). For comparison, t test or Mann Whitney are utilized. Categorical variables are expressed as their value and percentage (%). For their comparison, Fisher exact test is employed. For survival estimation, Kaplan Meier method was chosen. In all cases, a p value < 0.05 is considered with statistical significance. The software utilized was SPSS 21.0 (™).

RESULTS

Twenty patients underwent open re - anastomosis for VUAS after RP between July 2002 and June 2017. Demographic data is described in Table-1.

The median follow-up after ORA was 10 months (r 3 - 112).

The approach distribution was: perineal 10 patients (50%) and abdominal 10 (50%). The mean surgery time was 246.2 ± 35.8 minutes with no differences between approaches (perineal 248.9 ± 69; abdominal 229.5 ± 22.1, p 0.61). No significant intraoperative complications were recorded, no rectal or ureteral orifices injuries were evidenced and no patient required blood transfusion.

Figure 2 - Pre and post ORA cystourethrography in perineal approach.

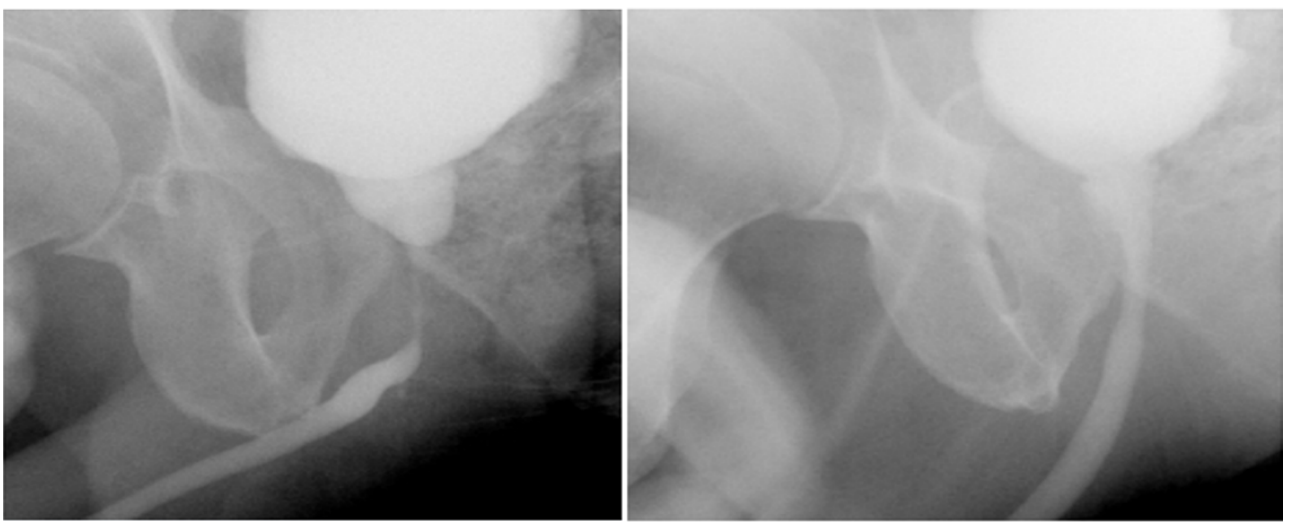


Figure 3 - Urethral lumen previous to re anastomosis by abdominal approach. Note that the pubectomy provide a comfortable surgical access to the stricture area.

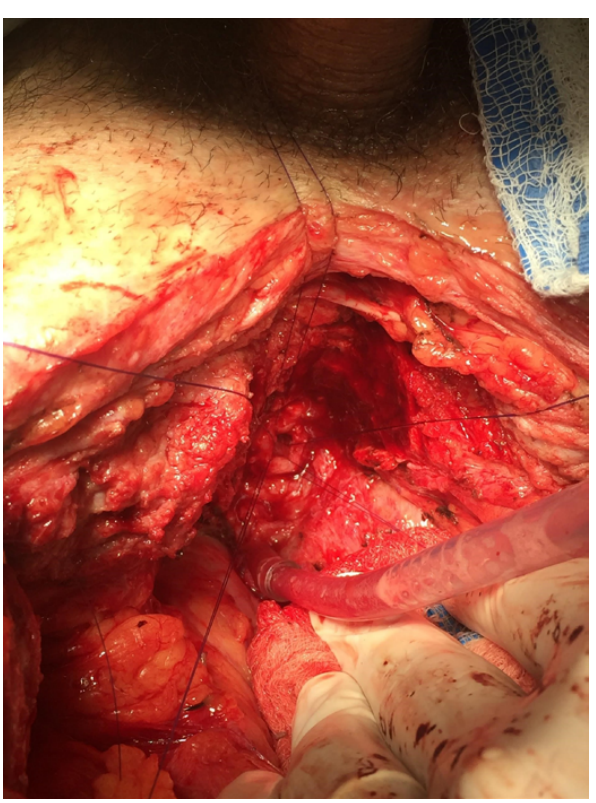
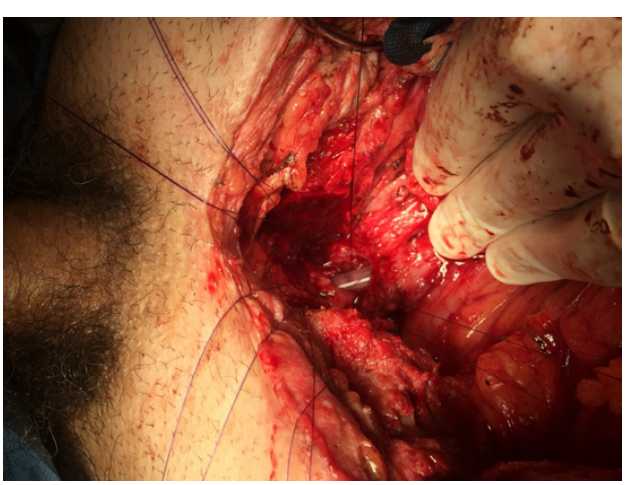


Figure 4 - Reanastomosis by abdominal approach.



Post operatory data is described in Table-2. Minor postoperative complications were similar in both groups. Length of hospital stay was higher in the abdominal approach group, where gait disorders were exclusively present. This gait disturbance is fully associated with partial pubectomy. Patients referred during the first 20 to 30 days, limp due to pelvic bone pain, needing help from a cane, with a spontaneous resolution within 30 days after surgery, only requiring nonsteroidal anti - inflammatory drugs (NSAIDs) orally.

Figure 5 - Pre and post ORA cystourethrography in abdominal approach.

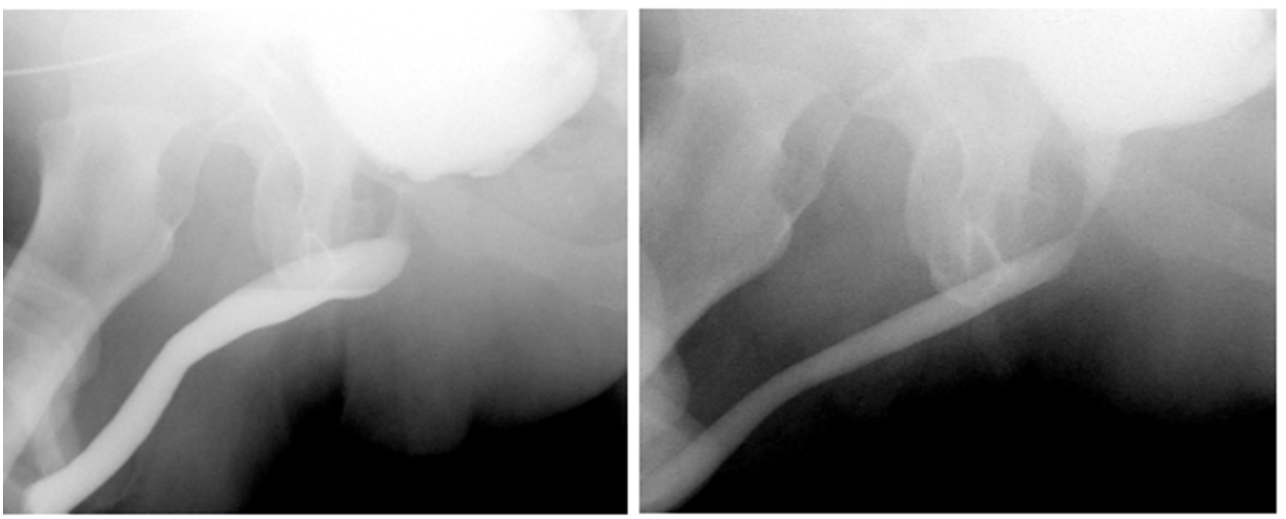


Table 1 - Demographic data.

Mean age years (sd)	63.7 (1.4)
Type of surgery (%):	
Radical prostatectomy	13 (65)
Laparoscopic radical prostatectomy	4 (20)
Salvage radical prostatectomy (post radiotherapy)	3 (15)
Adjuvant radiotherapy (%)	5 (25)
Comorbidities (%):	
Diabetes	2 (10)
Obesity	3 (15)
Smokers	4 (20)
Mean number of endoscopic treatments post RP (sd)	2.26 (1.8)

Success rate

The estimated 2 years primary success rate was 80% (95% IC 62.6 - 97.4). Median time to primary recurrence was 6 months (r 1 - 36). Of the 6 recurrences, 4 were in the perineal approach group and 2 in the abdominal approach group (p 0.329). Two of this six patients were irradiated patients (one in each group). Median follow-up time after primary procedure was 19.5 months (r 3 - 106). All recurrences were treated with one minimally invasive procedure (5 patients internal urethrotomy and 1 urethral dilatation). Only 9 patients had a follow-up longer than 24 months, in this population, after minimally invasive procedures, overall success rate was 89.9%.

Median follow-up after secondary procedure was 24 months (r - 12 - 108). During follow-up, 19 patients (95%) achieved mean Qmax of 19 mL / sg (r 13 - 32 mL / seg).

Table 2 - Post operatory data.

	Overall (n=20)	Perineal (n=10)	Abdominal (n=10)	p
Median hospital convalescent time, days (r)	4 (r 2-10)	3 (2-4)	4 (3-10)	0.03
Postoperative complications (%)	7 (35)	2 (20)	5 (50)	0.35
Clavien- Dindo I	3 (15)	1 (10)	2 (20)	
Clavien- Dindo II	4 (20)	1 (10)	3 (33.3)	
Disorders in the gait (%)	4 (20)	0	4 (40)	0.07

Urinary incontinence

All patients that underwent perineal approach were completely incontinent following re - anastomosis, and were treated with anti - incontinence devices or are scheduled for treatment. Three patients in the abdominal approach developed "de novo" urinary incontinence (p 0.003). One of these patients presented severe UI and was treated with AUS, this patients belonged to the radiated group. The other two underwent biofeedback therapy due to their mild UI, one of them with good response. After this treatment, 9 of 10 patients were continent (90%) (Table-3).

Erectile dysfunction

As regards erectile dysfunction, 19 patients presented this affection after RP. Only one patient had normal erectile function post RP, and this condition was maintained after ORA.

DISCUSSION

Vesicourethral stenosis after radical prostatectomy is an uncommon and difficult complication to treat. Literature analysis, in some cases with an antiquity greater than 10 years, describes an incidence that varies from 0.5 to 32 % (2, 3, 5-9, 17). VUAS etiology is not yet clear; inadequate contact mucosa - mucosa appears to be the genesis of this complication and most important risks factors related are smoke habits, radiotherapy, obesity, previous TURP, surgeon unexperienced, hematoma and urinary leak (5, 7, 9, 13).

Endoscopic management in non - obliterative VUAS after RP appears to be the first option. Controversy exists regarding which endoscopic approach is better. Recently, LaBossiere et al., compared the results obtained with different

Table 3 - UI treatment and evolution by approach.

Treatment	Perineal approach (Evolution)	Abdominal approach (Evolution)
Artificial Urinary Sphincter	2 patients (1 extrusion: required a new AUS)	1 patient (Actually continent)
Sling	2 patients (Actually continent)	0
Biofeedback	1 patient (Good response:1 pad/day)	2 patients (1 Good response:1 pad/day) (1 Not response:3or more pads/day)
No treatment by the time the data was analyzed	5 patients (2 planning Anti-incontinence device)	0

endoscopic modalities treatment for VUAS and report that holmium laser incision appears to have more success compared to other modalities (2). Some authors suggest the use of intralesional antiproliferative substances improves outcomes (11, 13, 18). Endoscopic approach in obliterated VUAS is not only non - effective but also unsafe (18, 19).

Despite these results, approximately 10% of the patients will not respond to endoscopic treatments (2). In these patients, the options frequently considered are urinary diversion, suprapubic cystostomy and open re-anastomosis. This last procedure is reserved for healthy and well - motivated patients and has the advantage of preserving the bladder with the intrinsic benefits.

ORA can be accomplished by perineal, abdominal and abdominal / perineal approach (12, 13).

Perineal approach offers the advantage of being free of previous surgeries with unscarred tissue, however the most important problem is the trans - sphincteric mobilization of the urethra and consequent UI. Recently, Cavalcanti et al. described a series of 48 patients with VUAS addressed by perineal approach. Twenty four of them (50%) presented UI (20). In addition, Ivaz et al., stated that all patients must be counselled that this will almost certainly be a two - stage reconstruction, the first to unblock them by revision of the vesicourethral anastomosis and then secondly to implant an artificial urinary sphincter for the almost inevitable sphincter weakness incontinence following unobstruction (16). This is supported by our data, where all 10 patients that underwent perineal approach were incontinent following re - anastomosis and the majority of them were offered to receive an anti - incontinence treatment.

AUS is considered the gold standard for the treatment of UI after VUAS re - anastomosis by perineal approach. Despite the utility of the AUS, it is well known the association with complications and urinary incontinence post implantation vary between 12 and 40% (20-25). Recently, successful implantation (17 / 23 patients) has been reported with AUS for UI after perineal approach (15). In the majority of their patients the authors describe a double cuff was implanted and 4 cases needed revision or explantation. On the other hand, Nicolavky and colleges, reported that AUS cuff erosion occur only in patients with previous urethral mobilization by perineal approach (26). In our series, 2 patients in the perineal group, were implanted with a AUS, with one of them suffering cuff erosion.

Considering the VUAS is proximal to the sphincter, the abdominal approach would allow the re - anastomosis to be performed leaving the external sphincter intact and thus the patient's continence. Abdominal approach is considered more complex, since the need of an aggressive bladder mobilization and, in some cases, a wide pubectomy in a previous scarred surgical field. We do not report significant differences between approaches regarding surgery time, need of blood transfusion or minor postoperative complications. Length of hospital stay was higher in abdominal approach group, where gait disorders were exclusively present. As regards to this last complication, patients refer the first 20 to 30 days limp due to pelvic bone pain, with a spontaneous resolution within 30 days after surgery. Patients only required oral NSAIDs as analgesic. This complication is fully associated with pubectomy. Complete removal or incision of the pubis will adequately expose the posterior urethra and distal bladder neck but the stability of the pubis may be compromised. Literature describes children that suffered from chronic pain and gait disturbances after this procedure (27). Although gait disorders have full recovery, patients must always be advised before surgery if abdominal approach is chosen.

Even Wessels et al. (28) present a series with 100% of UI after ORA by abdominal approach; most recently Pfalzgraf et al. reported a 64% preserved continence after ORA with this approach (14), prevalence that seems to be similar to our series, where 7 of 10 (70%) patients that underwent abdominal approach preserved their urinary continence. In our report, in the 3 patients who developed de novo UI, just one required an AUS because he presented severe UI. The other two underwent biofeedback therapy due to their mild UI. After this treatment, 9 of 10 patients were continent (90%).

Overall, our stenosis free rate of ORA in the

treatment of recalcitrant VUAS after RP is 89.9% despite the approach with a median follow-up of 10 months (3 - 112). These results are similar to the ones reported in the literature, where different approaches achieved good results (12). When we look at the 9 patients with global follow-up more than 2 years, 4 (44.4%) were treated with minimally invasive procedures (median time 16.5 months, 2 abdominal and 2 perineal approach). In this patients success rate after minimally invasive treatment was 89.9% with a median follow-up after that treatment of 19.5 months.

We reported a set of complications that are different depending of the approach. In the abdominal group, the more frequent complication was related with the pubectomy. Four patients referred disorders in the gait for at least a month after surgery, with complete recovery after that period of time. We do not have clear explanation of these complications other than the stability of the pubis may be compromised after pubectomy. Another complication related to this approach is the presence of fistula (1 patient), event not observed in patients who underwent perineal approach.

This paper has some limitations. Due to the low prevalence of this kind of pathology, the number included is low, so conclusions could not be so strong. Follow-up median time was 10 months, with half of patients with less than one year of follow--up, which is too short for a cohort study. This short follow-up may lead us to bias because overestimation of success rate, even when we inform success rate of the sample of patients with follow-up larger than 2 years. Follow-up after minimally invasive treatment may be too short to establish real success rate which is the problem of this rare pathology.

On the other hand, we consider our report as a novel task. There are few published papers about this issue on Latin American patients. In the translational medicine era, having publications of this sort of pathologies is a big help for urologists to know how to deal with them.

CONCLUSIONS

Open treatment of vesicourethral anastomosis has overall success rate of 89.9% despite the approach. All patients with perineal approach remained incontinent. On the other hand, abdominal approach presents an incontinence prevalence of 10%. No major complications were observed in any procedure. After abdominal approach, gait disorders may occur with complete recovery achieved in a month as average time.

CONFLICT OF INTEREST

None declared.

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Robot assisted radical prostatectomy in kidney transplant recipients: surgical, oncological and functional outcomes of two different robotic approaches

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ABSTRACT

Background: To date, few series on robot-assisted radical prostatectomy (RARP) in kidney transplant recipients (KTRs) have been published.
Purpose: To report the experience of two referral centers adopting two different RARP approaches in KTRs. Surgical, oncological and functional results were primary outcomes evaluated in the study.
Material and methods: We retrospectively analyzed data from 9 KTRs who underwent transperitoneal RARP or Retzius-sparing RARP for PCa from October 2012 to April 2016. Data were reported as median and interquartile range (IQR). Pre- and postoperative outcomes were compared by non-parametric Wilcoxon signed-rank test. Significant differences were accepted when $p \leq 0.05$. Overall survival was assessed using Kaplan-Meier method.
Results: Four KTRs underwent a T-RARP and 5 a RS-RARP. Patient median age was 60 (56-63) years. Charlson comorbidity index was 6 (5-6). Preoperative median PSA was 5.6 (5-15) ng / mL. Preoperative Gleason score (GS) was 6 in 5 patients, 7 (3 + 4) in 3, and 8 (4 + 4) in one. Pre- and postoperative creatinine were 1.17 (1.1; 1.4) and 1.3 (1.07; 1.57) mg / dL ($p = 0.237$), while eGFR was 66 (60-82) and 62 (54-81) mL / min / 1.73m2 ($p = 0.553$), respectively. One (11.1%) Clavien-Dindo grade II complication occurred. Two extended template lymphadenectomies were performed, both with nodal invasion. These two patients experienced a biochemical recurrence and were subjected to RT. Two patients (22.2%) had PSMs. Median follow-up was 42 months. Seven patients (77.8%) were continent, 5 (55.6%) were potent. Two (22.2%) patients died during follow-up for oncologic unrelated causes.
Conclusions: Our series suggests that both RARP approaches are safe and feasible techniques in KTRs for PCa.

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Keywords:
Kidney Transplantation; Prostatic Neoplasms; Prostatectomy; Robotics

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INTRODUCTION

In the last decades, a longer and qualitatively better life has been granted to kidney transplant recipients (KTRs) (1).

However, a higher rate of carcinogenesis has been described with an increase of the risk of malignant transformation by three to five folds compared to age-matched controls (2).

In these patients, prostate cancer (PCa) represents the most common tumor among genitourinary malignancies (3). Despite several series have been published, the real incidence of localized PCa in these cohorts remains unclear, ranging from 0.72% to 3.1% (4, 5). Recently, a large population of 123.280 transplant recipients has been investigated and PCa was identified as the most frequent organ-confined neoplasia, diagnosed in 0.82% patients (6).

Although different options have been proposed for the treatment of PCa in KTRs, such as surgery, radiotherapy and brachytherapy (7), radical prostatectomy remains the preferred option. Reasons in favor of surgery could be ascribed to possible complications associated to radiation treatment (RT) in this group of patients (ie. nephritis, ureteral anastomosis strictures, avascular necrosis of the femoral head).

To date, few data have been reported regarding active surveillance (AS) or watchful waiting (WW) for PCa in KTRs (8). However, non-active treatments would be perhaps adopted in the future even in this specific low risk PCa population.

Though in small series, almost all approaches for radical prostatectomy have been described, including retropubic, transperineal, and laparoscopic (4, 9-11). However, radical prostatectomy is more complex in KTRs due to previous peritoneal dialysis, transplant surgery, graft location and immunosuppression. In 2008, Jhaveri et al. described the first robot assisted radical prostatectomy (RARP) in a patient with a kidney graft. To our knowledge, only limited series have been published about RARP in KTRs (4, 5, 7, 11-15).

The aim of the current study is to evaluate safety, feasibility and efficiency of two different RARP techniques in KTRs, performed in two high-volume referral centers, and to describe intra- and post-operative outcomes, analyzing short- and medium-term follow-up oncological and functional outcomes.

MATERIALS AND METHODS

From October 2012 to May 2016, nine patients previously subjected to renal transplantation underwent RARP. Four of them, experienced a trans-peritoneal RARP (T-RARP); five a Retzius-sparing RARP (RS-RARP); all of them were diagnosed with a localized PCa.

All data were prospectively collected in two different customized databases and retrospectively analyzed.

Baseline demographic features, surgical, oncological and functional outcomes were investigated and complications were evaluated according to the Clavien-Dindo scale (16).

Potency was defined as erections allowing satisfying penetrations. Continence recovery was assessed according to ICIQ criteria (17).

Description of the techniques

Patients were placed in lithotomy position, with a 27 to 30 degrees Trendelemburg inclination. All pressure points were carefully padded in order to avoid vascular and nervous injuries. Before the port placement, a bladder catheter was positioned.

A standardized four-arm robotic configuration was used in all patients, either with the robotic da Vinci® Si or Xi systems, both placed caudally between the legs: a total of 6 ports were used, 3 for the robotic arms, 1 for the camera and 2 for the bedside assistant (one of 12mm and one of 5mm).

The placement of the third robotic arm or the 12mm assistant port was modified, medially and cranially respect to the standard set, in the renal transplant recipients to avoid trauma to the graft as represented in Figures 1 and 2.

Lymphadenectomies were carried out according to the preoperative risk of lymph node invasion assessed according to the updated Briganti nomogram (18).

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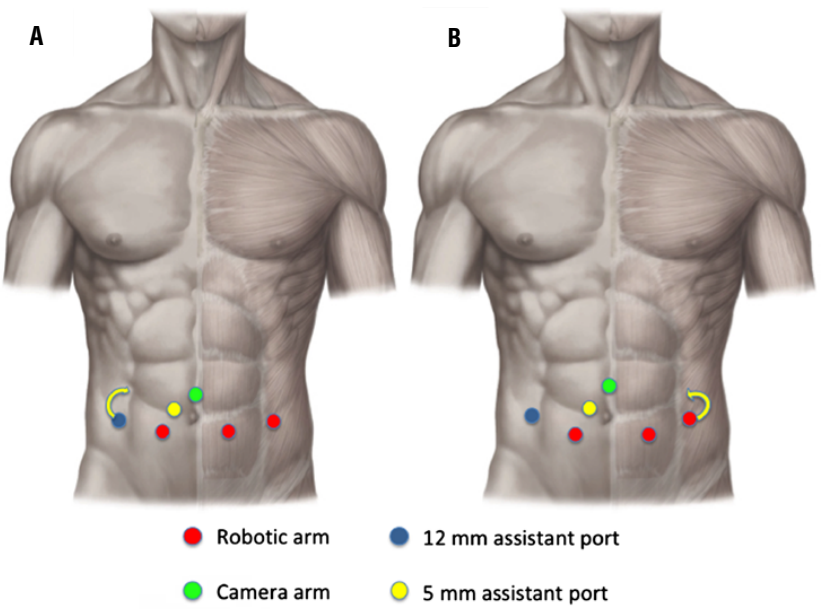
In two KTRs, the bedside assistant stood on the left side, instead of on the right, to avoid trauma to the right positioned kidney graft during the laparoscopic instruments insertion.

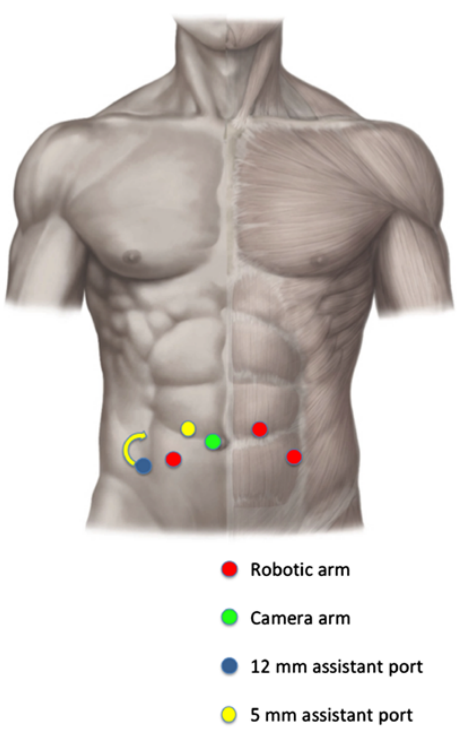
The peritoneal incision, external to the umbilical ligaments, was tailored according to the transplant side; the remaining procedure was conducted equally to our standardized RARP procedure.

Figure 1 - Robotic and assistant port positioning for T-RARP.



A) The placement of the 12 mm assistant port was modified, medially and cranially respect to the standard set, in case of right kidney graft location. B) The placement of the third robotic arm was modified, medially and cranially respect to the standard set, in case of right kidney graft location.

Figure 2 - Robotic and assistant port positioning for RS-RARP.



The placement of the 12 mm assistant port was modified, medially and cranially respect to the standard set, in case of right kidney graft location.

All patients underwent a nerve sparing procedure, two patients only anterograde and two anterograde and retrograde.

In all patients, a posterior musculo-fascial reconstruction after radical prostatectomy was performed as described by Coelho et al. (19) and no lymphadenectomies were carried out.

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The bedside assistant was placed on the right side of the patient. In case of a right-sided kidney transplant, the 12mm assistant port was placed more cranially. After the docking, the Retzius-sparing surgery was conducted as previously described (20), without modifications from the standard protocol: the peritoneal incision was performed on the rectovesical pouch, where the surgical field was intact from previous surgeries and the kidney was placed distant. No posterior reconstruction techniques have been used.

One monolateral and one bilateral lymphadenectomy were performed, adopting an extended template. The main limitation in performing a bilateral template was ascribed to the previous vessels dissection and vascular anastomosis for the kidney graft. Moreover, our dissection resulted

very difficult due to the healing adhesions found in the perinodal fat.

Statistical analysis

Data are reported as median and interquartile range (IQR). Pre- and postoperative outcomes were compared by non-parametric Wilcoxon signed-rank test. Significant differences were accepted when $p \leq 0.05$. Overall survival (OS) was assessed using Kaplan-Meier method.

Statistical analysis was performed using SPSS, version 20 (IBM, New York, NY, USA).

RESULTS

Pre-, intra- and postoperative outcomes are showed in Tables 1 and 2. Data are reported as median and interquartile range (IQR). Patient age at surgery was 60 (56-63) years, with a BMI of 25.7 (24.2-27.7) kg / m^2. The interval between renal transplantation and RARP was 9 years (6-22): renal graft was sited on the right iliac fossa in 7 (77.8%) patients and on the left for the remaining 2 (22.2%). Charlson comorbidity index was 6 (5-6). In the preoperative assessment median PSA resulted of 5.6 (5-15) ng / mL, while the clinical stage was T1c in 4 (44.5%) patients, T2a in 3 (33.3%), T2c and T3b for the remaining two. At the prostate biopsy, the Gleason score was established as 6 (3 + 3) in 5 (55.6%) patients, 7 (3 + 4) in 3 (33.3%) patients, and 8 (4 + 4) in the remaining one (11.1%). Among the 5 patients diagnosed with a GS of 6 (3 + 3), 2 had oncologic characteristic adequate for AS according to PRIAS criteria (21), but both refused the surveillance program. Due to preoperative serum creatinine of 6.7 mg / dL, one (11.1%) patient was subjected to hemodialysis the day before radical prostatectomy. No significant difference was described comparing serum creatinine levels before and after surgery, accounted respectively for 1.17 (1.1-1.4) and 1.3 (1.07-1.57) mg / dL ($p = 0.237$). Furthermore, no significant difference was described for eGFR calculated as 66 (60; 82) and 62 (54; 81) mL / min / 1.73m2 respectively before and after surgery ($p = 0.553$). In two (22.2%) patients chronic kidney disease status (CKDS) worsened of 1 point after surgery, while

Table 1-Robotic and assistant port positioning for T-RARP.

Variables		
Age, yrs (median, IQR)	60	(56-63)
BMI, kg/m^2 (median, IQR)	25.7	(24.2-27.7)
CCI (median, IQR)	6	(5-6)
Time from transplantation, yrs (median, IQR)	9	(6-22)
Creatinine, mg/dL (median, IQR)	1.17	(1.1;1.4)
PSA, ng/mL (median, IQR)	5.6	(5-15)
Gleason score Sum (Nº, %)	(3+3)	5 (55.6%)
	(3+4)	3 (33.3%)
	(4+4)	1 (11.1%)
Clinical Stage (Nº, %)	T1c	4 (44.5%)
	T2a	3 (33.3%)
	T2c	1 (11.1%)
	T3a	1 (11.1%)

Abbreviations: **yrs =** Years; **IQR=** Interquartile range; **BMI =** Body mass index; **CCI =** Charlson Comorbidity Index; **PSA =** Prostate Specific Antigen

Table 2-Robotic and assistant port positioning for RS-RARP.

Variables		
Operative time, min (median, IQR)	160	(145-183)
EBL, mL (median, IQR)	100	(100-200)
Length of stay, days (median, IQR)	4	(3-6)
Nº of LADs (Nº, %)	2 (22.2%)	
Nº of positive LADs (Nº, %)	2 (22.2%)	
Days of catheterization (median, IQR)	7	(6-8)
Complications by Clavien scale (Nº, %)	Grade II: 1 (11.1%)	
Gleason score Sum (Nº, %)	(3+3)	4 (44.5%)
	(3+4)	3 (33.3%)
	(4+3)	2 (22.2%)
Pathologic Stage (Nº, %)	pT2a	1 (11.1%)
	pT2c	6 (66.7%)
	pT3a	1 (11.1%)
	pT3b	1 (11.1%)
PSMs (Nº, %)	2 (22.2%)	
BCR (Nº, %)	2 (22.2%)	
Potency recovery rate (Nº, %)	5 (55.6%)	
Continence recovery rate (Nº, %)	7 (77.8%)	
Last follow up serum creatinine, mg/dL (median, IQR)	1	(1-2.7)

Abbreviations: **IQR =** Interquartile range; **EBL =** Estimated blood loss; **LADs =** Lymphadenectomies; **PSMs =** Positive surgical margins; **BCR =** Biochemical recurrence

in one (11.1%) patient we detected a 1-point improvement. No intraoperative complications were reported. Overall, operating time was 160 (145-183) minutes, with an estimated blood loss of 100 (100-200) mL. Six (66.7%) patients were subjected to a nerve sparing procedure. Prostate weight was 40 (39-45) g. Median hemoglobin decrease was 2.6 (2.15-3.2) and no blood transfusion was necessary. One (11.1%) Clavien-Dindo grade II complication was described due to a systemic inflammatory syndrome for urinary tract infection. The hospital stay consisted in 4 (3-6) days, while the days of catheterization were 7 (6-8) days.

No changes in immunosuppressive regimes were reported in pre- or postoperative periods. Regarding calcineurin inhibitors (tacrolimus or cyclosporine), serum levels were daily obtained during the hospital stay and therapy was adjusted as necessary. Pathological analysis reported Gleason score 6 (3 + 3) in four patients (44.5%), 7 (3 + 4) in three (33.3%) and 7 (4 + 3) in the other two (22.2%). One patient (11.1%) was pT2a, six patients (66.7%) pT2c, one (11.1%) pT3a and the last one (11.1%) pT3b. In two patients an extended lymph node dissection was performed, and in both patients a lymph node invasion was assessed. In one case a bilateral lymphadenectomy was perfor-

med with a lymph node yield of 19 nodes, 3 of them positive for neoplastic invasion. In the other case, a monolateral lymphadenectomy was conducted with a lymph node yield of 3 nodes, 1 of them positive for neoplastic invasion. These two patients experienced a biochemical recurrence (BCR) (PSA > 0.2 ng / mL) and were subjected to RT. Two patients (22.2%) had positive surgical margins, one of them was focal. All patients reached at least 12 months of follow-up (median 42 months); 7 (77.7%) were continent, the remaining 2 patients were affected by a moderate incontinence; 2 (22.2%) patients were potent, while other 3 (33.3%) of them reached a potency recovery with PDE-5 inhibitors administration. At last follow up median serum creatinine accounted for 1 (1; 2.7) mg / dL, and no significant difference was described with pre preoperative one (p = 0.237). Two (22.2%) patients died for oncologic unrelated causes.

DISCUSSION

Although widely debated, a greater incidence of PCa was described in transplanted patients (22), with higher frequencies of advanced malignancies and worse disease specific survival (23).

Moreover, thanks to immunosuppression regimen improvements, survival expectancy after kidney transplantation has increased of more than 10 years, (12) enlarging the number of recipients older than fifty years old, and making PCa handling as important as in general population (1).

Generally, alteration of normal tissue's planes caused by previous retroperitoneal surgery and pelvic location of kidney graft are frightening factors that preclude RT in order to avoid adverse events (ie. ureteral stenosis, actinic pyelonephritis and gastrointestinal toxicity) (5, 24).

In 2004, Mouzin et al. published a study in which 8 KTRs underwent external beam RT as primary therapy for localized PCa. In two patients (25%) a significant obstruction of the terminal ureter was described, and one patient (12.5%) had a decrease in renal graft function (24). Moreover, two patients (25%) had BCR after a mean follow-up period of 28 months.

On the contrary, more recently Iizuka et al. showed no severe adverse events in 4 KTRs treated with RT (5).

Typically, localized PCa in KTRs had been treated performing a radical retropubic-prostatectomy (9). However, a surgical treatment could not be thought free from challenges and complications. Most common hitches were graft injuries, including also ureter and vessels, high incidence of intraperitoneal adhesions in patient subjected to peritoneal dialysis, difficulties in performing a vesical-urethral anastomosis due to bladder descent limitation caused by the shortness of transplant ureter (25).

In 2006, Shah et al. described the first series of laparoscopic radical prostatectomy (LRP) in KTRs (26). Despite some studies depicted LRP as safe and feasible in the treatment of PCa in transplant recipients, Robert et al. reported an incidence of rectal injury clearly higher than in general population (22.2 vs. 1.8%, p = 0.022) (27).

Since its advent, robotic approach overcame the technical limitations that have characterized the laparoscopic surgery. Particularly in presence of pelvic graft, the wristed instruments allow for easier suturing and dissection avoiding the graft hindrance flexing over it.

In 2008, Jhaveri et al. reported the first case of the RARP in KTRs (4). Since then, few studies, with small cohort, were published regarding the use of robotic approach to treat localized PCa in this population (Table-3).

To our knowledge, our series represents the second largest cohort of KTRs treated with RARP, and the only multi-institutional study that includes two different techniques.

Despite the aforementioned advantages, RARP remains a challenging surgery in these patients. Several authors have described some technical modifications necessary to overcome the graft's impediment; for example, Smith et al. and Polcari et al. adopted assistant ports placement contralateral to renal graft (12, 13), while Ghazi et al. and Moreno et al. modified the 6 ports setting into a 5 ports arrangement, performing RARP without a robotic arm. (7, 14); some others, instead, (11, 15) proved the modification of the port sites to be useless.

In our series, during T-RARP assistant, ports were placed contralateral to renal graft, and, as suggest by Jhaveri et al. (4), the robotic arm on

Table 3-Overall survival Kaplan-Meier curve analysis.

Authors	Year	Nº of patients	Surgical approach	Operating time, min	Estimated blood loss, mL	Complications Clavien-Dindo	Hospitalization, days	Catheterization, days	PSM, nº (%)	BCR, nº (%)
Jhaveri et al.	2008	1	Transperitoneal	200	400	No	2	7	No	No
Smith et al.	2011	3	Transperitoneal	322	75	No	2.3	-	1 (33%)	NO
Polcari et al.	2012	7	Transperitoneal	186	-	Grade II: 3 1 Haematuria 1 Urosepsis 1 Atrial fibrillation	1.8	8.1	2 (28.6%)	1 (14.3)
Wagener et al.	2012	1	Transperitoneal	220	300	No	-	(4 weeks)	No	No
Ghazi et al.	2012	1	Transperitoneal	130	125	No	-	10	No	-
Le Clerc et al.	2015	12	Transperitoneal	241	648		-	-	3 (27.3)	2 (16.7)
Moreno et al.	2015	4	Transperitoneal	196	-		3.2	10	2 (50)	1 (25)
Iizuka et al.	2016	3	Transperitoneal	162	52	Grade II: 1	-	9.3	No	1 (33.3)
Mistretta et al.	2017	9	Cumulative:	160	100		4	7		
			T-RARP: 4	170	100	No	5	6	No	No
			RS-RARP: 5	150	100	Grade II: 1 1 Urosepsis	3	8	2 (22.2%)	2 (22.2)

Abbreviations: **RARP =** Robot-assisted radical prostatectomy; **T-RARP =** Transperitoneal-RARP; **RS-RARP =** Retzius Sparing-RARP; **PSMs =** Positive surgical margins; **BCR =** Biochemical recurrence

the side of the graft was slightly lifted up in order to avoid injuries.

For the RS-RARP instead, only the robotic arm on the side of the graft was moved cranially and laterally respect to the standard setting.

Despite the graft hindrance and the setting modifications, we described comparable operative times in respect to the standard RARP. Furthermore, no intraoperative complications were reported and no blood transfusions were required.

Previous studies reported variable rate of complications (43%), (4, 5, 7, 11-15) maybe results of the small samples size, including urosepsis, hematuria, atrial fibrillation, conversion to laparotomy.

In the current study, we reported only a single case (11.1%) of urosepsis, promptly resolved with appropriate therapy. Noteworthy, no surgical or medical injuries were assessed regarding graft function. In fact, no significant differences in se-

rum creatinine levels were observed between pre- and postoperative settings (p = 0.237), or at the last follow-up (p = 0.237). Similarly, no significant differences were found regarding pre- and postoperative CKDS status.

Regarding the oncological outcomes, pathological analysis described a Gleason score 6 (3 + 3) in 44.5% of patients, 7 (3 + 4) in 33.3% and 7 (4 + 3) in the 22.2%, describing 4 upgrading and 2 downgrading in respect to Gleason score assessed at preoperative prostatic biopsy.

These data underline the problem of RARP for low risk PCa patients, particularly in frail patients such as KTRs. Few studies are reported regarding AS for PCa in transplant recipients. In particular, AS was described only in one study for one patient with low-risk disease (28), WW in one study for four patients in total (29).

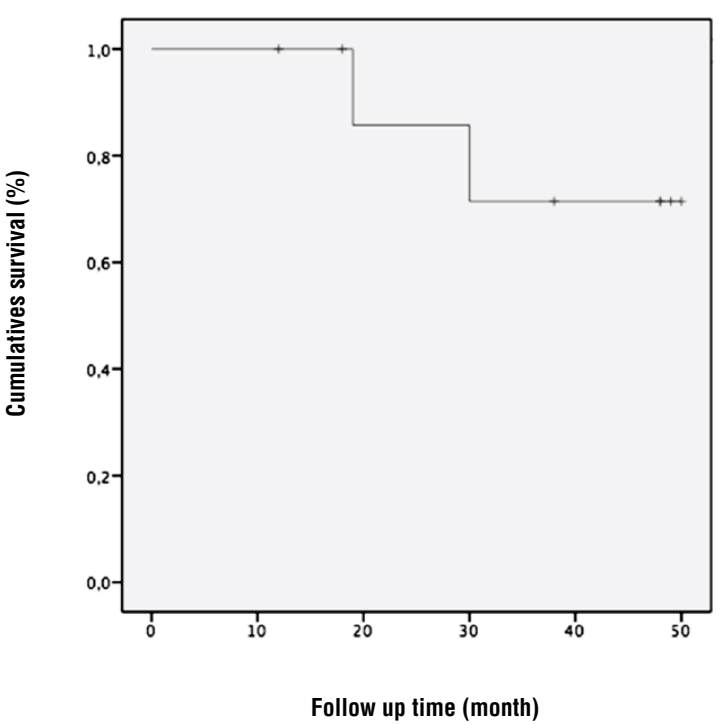
In our series AS was proposed to the two patients that satisfied preoperative PRIAS criteria (21), but both of them refused the surveillance program. Although, the immunomodulation and the subsequent impaired spontaneous cancer control should be considered in this population.

Despite the short follow-up and the small size of the series, our study described oncologic outcomes concordant with the ones reported in literature. In the general population, PSM rate of patient treated with RARP for localized PCa ranged from 14.1% to 29% (30). In the previous studies regarding RARP in KTRs PSM rate was reported as 0-50% (4, 5, 7, 11-15). In our study two patients (22.2%) had a PSM, one of them focal.

In general population, BCR free survival rates at 3 years were reported at 96.3% (31). In our study, two patients (22.2%) experienced BCR and underwent radiotherapy. These data are similar to those of previous series of KTRs subjected to RARP. Moreover, high PSA levels and palpable neoplasia at digital rectal examination had been assessed in these two patients before surgery and a nodal invasion was determined at final histology.

Lastly, two patients (22.2%) died due to cancer unrelated causes. Curve regarding overall survival is showed in Figure-3.

Figure 3 - Overall survival Kaplan-Meier curve analysis.



However, similarly to PSM rate and BCR, it is difficult to analyze data regarding survival rate, and these high frequencies could be attributed to the limited number of cases in the series.

A good continence recovery was described in previous studies (4, 7, 11-13). Our data agree with the former assessing a complete continence recovery of 7 out 9 patients (77.8%). In the remaining two patients a moderate incontinence (17) was described. Noteworthy, one of these patients was subjected to adjuvant RT influencing the continence recovery.

Our study is the first reporting data on erectile function recovery. KTRs seem to be associated with higher rate of erectile dysfunction (32). The nerve sparing approach could result even more challenging if performed in KTRs.

In general population, potency recovery rate at one year after the surgical procedure was assessed ranging from 29.6% to 77.6% (33, 34). In the current study 6 patients (66.7%) received a nerve-sparing procedure (4 bilateral, 2 monolateral), and 5 (55.6%) achieved a potency recovery, with or without PDE5i intake, sufficient to have sexual intercourses.

The current study has some limitations due to the small sample size. However, although in future the incidence of PCa could increase in KTRs, nowadays it remains limited. This issue imposes to treat the pathology in referral high volumes centers, by expert surgeons.

Second limitation is the retrospective nature of the analysis. However, as previously stated the rarity of KTRs patients affected by PCa makes difficult to complete a randomized prospective trial.

CONCLUSIONS

The current study's results suggest that both RARP approaches adopted at our institutions may be safely applied in KTR patients. A low morbidity and overall good surgical outcomes were reported without any major complication. Oncologic and functional outcomes showed are comparable with those of general population patients subjected to RARP. However, robot-assisted radical prostatectomy still remains a challenging surgery in KTRs, and should be performed by expert robotic surgeons, in a tertiary referral center. Furthermore, a more consistent patient cohort is needed to confirm our results.

ABBREVIATIONS

BCR = biochemical recurrence
CKDS = chronic kidney disease status
IQR = interquartile range
KTRs = kidney transplant recipients
PCa = prostate cancer
RARP = robot-assisted radical prostatectomy
RS-RARP = Retzius sparing RARP
RT = radiation treatment
T-RARP = transperitoneal RARP

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Is moderate hypofractionation accepted as a new standard of care in north america for prostate cancer patients treated with external beam radiotherapy? Survey of genitourinary expert radiation oncologists

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ABSTRACT

*Introduction: S*everal recent randomized clinical trials have evaluated hypofractionated regimens against conventionally fractionated EBRT and shown similar effectiveness with conflicting toxicity results. The current view regarding hypofractionation compared to conventional EBRT among North American genitourinary experts for management of prostate cancer has not been investigated.

Materials and Methods: A survey was distributed to 88 practicing North American GU physicians serving on decision - making committees of cooperative group research organizations. Questions pertained to opinions regarding the default EBRT dose and fractionation for a hypothetical example of a favorable intermediate - risk prostate cancer (Gleason 3 + 4). Treatment recommendations were correlated with practice patterns using Fisher's exact test.

Results: Forty - two respondents (48%) completed the survey. We excluded from analysis two respondents who selected radical hypofractionation with 5 - 12 fractions as a preferred treatment modality. Among the 40 analyzed respondents, 23 (57.5%) recommend conventional fractionation and 17 (42.5%) recommended moderate hypofractionation. No demographic factors were found to be associated with preference for a fractionation regimen. Support for brachytherapy as a first choice treatment modality for low - risk prostate cancer was borderline significantly associated with support for moderate hypofractionated EBRT treatment modality (p = 0.089).

Conclusions: There is an almost equal split among North American GU expert radiation oncologists regarding the appropriateness to consider moderately hypofractionated EBRT as a new standard of care in management of patients with prostate cancer. Physicians who embrace brachytherapy may be more inclined to support moderate hypofractionated regimen for EBRT. It is unclear whether reports with longer follow-ups will impact this balance, or whether national care and reimbursement policies will drive the clinical decisions. In the day and age of patient - centered care delivery, patients should receive an objective recommendation based on available clinical evidence. The stark division among GU experts may influence the design of future clinical trials utilizing EBRT for patients with prostate cancer.

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INTRODUCTION

The standard eight-to-nine week course of conventional external beam radiation therapy (EBRT) for prostate cancer although effective, disrupts patients' normal lives, causes financial toxicity to patients and places a significant financial strain on the healthcare system. For these reasons, hypofractionated radiation therapy (RT), which involves larger radiation doses administered over an overall shorter time period, has increased in popularity, and has been established in other disease sites, such as breast cancer, bone metastases, bladder cancer, glioblastoma and non - small cell lung cancer (1-5). Four randomized clinical trials have compared moderately fractionated regimens to conventionally fractionated RT in prostate cancer (Table-1) (6-11). With 5-years of follow-up, none revealed inferiority of hypofractionation regarding the treatment outcomes, and the toxicity reports are contradictory, with no overwhelming and reproducible toxicity associated with a moderately hypofractionated regimens using 2.5 to 3 Gy per fraction. We sought to determine the current view of moderate hypofractionation among North American genitourinary (GU) radiation oncology experts due to their influence in shaping the direction of national guidelines.

MATERIALS AND METHODS

Survey design and deployment

The survey was designed to assess the opinions of GU experts on the default EBRT dose and fractionation for a hypothetical patient with a favorable - intermediate risk prostate cancer who would require by most current conventions EBRT to prostate alone without prophylactic irradiation of pelvic lymph nodes. Three fractionation schemes were offered as choices: conventional fractionation (78 Gy in 2 Gy fractions, 79.2 Gy in 1.8 Gy fractions or equivalent), moderate hypofractionation (70 Gy in 2.5 Gy fractions or equivalent), or SBRT / radical hypofractionation (5 - 12 fractions or equivalent). The study was approved by IRB and electronically sent to 88 North American GU oncology physicians, who serve on cooperative group research organizations such as NRG Oncology. The survey was designed and hosted by Research Electronic Data Capture (REDCap), and contained screening questions to ensure respondents were currently practicing, not in training, and specializing in GU oncology (12). A copy of the survey is available in the Appendix 1.

Statistical analysis

Based on responses, participants were categorized as "supporters" or "opponents" of moderate hypofractionation. For the purposes of this study, only responders choosing conventional fractionation or moderate hypofractionation were included. Fisher's exact test was used to determine whether treatment recommendations were correlated with practice patterns. R (R version 3.3.3 (2017-03-06)) was used for all data analysis. Statistical significance was set at $p < 0.05$.

RESULTS

Forty - two of the 88 radiation oncologists completed the survey, of whom 40 (95.2%) recommended either conventional fractionation or moderate hypofractionation; two (4.8%) recommended stereotactic body radiation therapy (SBRT) (Figure-1) and were excluded from the analysis. Of 40 analyzable respondents, 23 (57.5%) recommended conventional fractionation and 17 (42.5%) recommended moderate hypofractionation.

No demographic factors (years in practice, geographic location of residency, geographic location of practice, monthly patient volume, practice type) as well as other clinical positions (active surveillance recommendation preference, brachytherapy boost advocacy, self-identification as an expert brachytherapist, likelihood of considering stereotactic body RT for oligometastatic disease, likelihood of prophylactically irradiating pelvic lymph nodes, support of advanced imaging techniques) were significantly associated with support of moderate hypofractionation. Only the choice of brachytherapy as a preferred

treatment option for patients with low - risk prostate cancer approached significance for recommendation of hypofractionation (p = 0.089) (Table-2).

DISCUSSION

Biological considerations of a markedly lower alpha / beta ratio of prostate cancer in comparison to surrounding normal tissues led researchers to clinical investigation of hypofractionated regimens in management of patients with prostate cancer with EBRT (13). Four large international randomized clinical trials have established non - inferiority of moderate hypofractionation (2.5 - 3 Gy per fraction), with varying toxicity results, some supporting conventional, others hypofractionated regimens, but none reporting overwhelming toxicity within the 5 - years of a follow-up period (Table-1) (6-11).

The degree of acceptance / rejection of treatment modalities in North America is to a significant extent shaped by opinions of leading academic physicians who define and periodically update national treatment guidelines, author consensus statements and shape the future clinical trial protocols. Because of this influence, we sought to determine the acceptance of hypofractionation for prostate cancer among North American GU radiation oncology experts (14).

The results of this study indicate that hypofractionated EBRT, defined as 70 Gy in 2.5 Gy fractions or an equivalent regiment, has made significant inroads among North American GU experts in the treatment of prostate cancer, as more than 40% of experts recommended hypofractionated EBRT as their preferred EBRT treatment modality. Nevertheless, 55% of experts still consider conventionally fractionated EBRT as an unchallenged standard of care. Physicians who embrace a shorter treatment modality (brachytherapy), despite possible increase in acute toxicity - also tend to support hypofractionated EBRT. The relatively even duality regarding conventional versus hypofractionated treatment recommendation for intermediate - risk prostate cancer despite the four randomized trials already published on this topic (6-9) speaks to the issue that randomized trials do not necessarily change the standard of care, particularly in the United States, and a significantly longer follow-up is required; this duality is reflected in the most updated clinically localized prostate cancer guidelines published jointly by the American Urological Association, American Society for Radiation Oncology (ASTRO), and the Society of Urologic Oncology (15, 16). Hypofractionation in breast cancer similarly was adopted in other countries much sooner than in the United States, where ASTRO consensus statements, educational sessions and even direct advertisement to patients regarding hypofractionated options and their non - inferiority, led to final acceptance of hypofractionation as a new standard of care. It is unclear whether reimbursement system in the U.S. is partially responsible for a slower update of shorter treatment courses. Limitations of this study are relatively small sample size, despite an impressive (but still below fifty percent) response rate, inability to capture a full range of options due to multiple choice format, and a lack of granularity in addressing the impact of racial demographic of patients being treated (17). Furthermore, the absence of decade - long toxicity and outcome data comparing conventional versus moderate hypofractionation provides an uncertainty of outcomes beyond the five years of currently published results (6-11).

In conclusion, there is currently a nearly even split between radiation oncology experts in North America recommending conventionally fractionated vs moderately hypofractionated EBRT for patients with prostate cancer, based on dramatically different interpretation of results of 4 randomized clinical trials. Longer follow-up of these trials may impact the balance, while national care and reimbursement policies may influence the accepted standard of care.

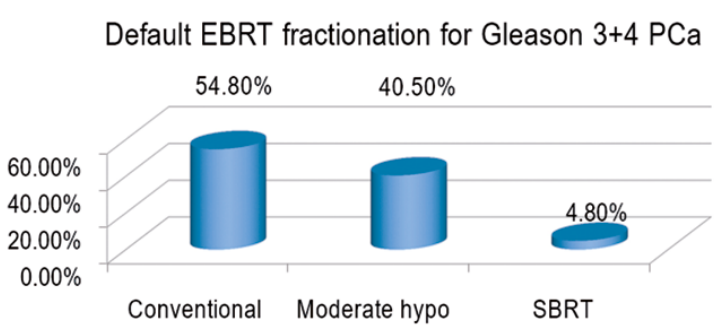
Table 1 - Summary of the four randomized clinical trials comparing hypofractionation (H-RT) with conventional fractionation (C-RT) for prostate cancer (OS = overall survival; DFS = disease-free survival; RFS = relapse-free survival; GU = genitourinary; GI = gastrointestinal; CI = confidence interval).

Trial	Hypofractionation regimen	Follow-up duration	Location	Differences in OS or DFS	Differences in GU toxicity between modalities	Differences in GI toxicity between modalities
RTOG 0415 (7)	2.5 Gy x 28	5 years	USA	No	No (late GU trended toward favoring C-RT: p=0.06)	Yes (late GI: p=0.002 favored C-RT)
CHHiP (8)	3 Gy x 20; 3 Gy x 19	5 years	UK, Ireland, Switzerland, New Zealand	No	No	Yes (acutely favoring C-RT; none by week 18)
PROFIT (6)	3 Gy x 20	5 years	Canada, Australia, France	No	No (acutely; late toxicity favored H-RT)	No (acutely; late toxicity favored H-RT)
HYPRO (9-11)	3.4 Gy x 19	5 years	Netherlands	No	Yes (H-RT inferior for acute and late grade 3+ toxicity)	Yes (H-RT inferior for acute but not late grade 3+ toxicity)

Trial	GU toxicity (H-RT)	GU toxicity (C-RT)	GI toxicity (H-RT)	GI toxicity (C-RT)	Disease control (H-RT)	Disease control (C-RT)
RTOG 0415 (7)	Early grade 2-4 GU = 147/545 Late grade 2-4 GU = 161/545	Early grade 2-4 GU = 145/534 Late grade 2-4 GU = 121/534	Early grade 2-4 GI = 58/545 Late grade 2-4 GI = 121/545	Early grade 2-4 GI = 55/534 Late grade 2-4 GI = 75/534	86.3% DFS (95% CI: 83.1-89.0)	85.3% DFS (95% CI: 81.9-88.1)
CHHiP (8)	Early grade 2-4 GU = 46-49% Late grade 2-4 GU = 6.6-11.7%	Early grade 2-4 GU = 46% Late grade 2-4 GU = 9.1%	Early grade 2-4 GI = 38% Late grade 2-4 GI = 11.3-11.9%	Early grade 2-4 GI = 25% Late grade 2-4 GI = 13.7%	85.9-90.6% biochemical/clinical failure freedom	88.3% biochemical/clinical failure freedom

PROFIT (6)	Early grade 2-4 GU = 185/608 Late grade 2-4 GU = 136/608	Early grade 2-4 GU = 183/598 Late grade 3-4 GU = 134/598	Early grade 2-4 GI = 99/608 Late grade 2-4 GI = 54/608	Early grade 2-4 GI = 62/598 Late grade 2-4 GI = 83/598	85% DFS	85% DFS
HYPRO (9-11)	Early grade 2-4 GU = 75/410 Late grade 2-4 GU at three years = 163/395	Early grade 2-4 GU = 73/410 Late grade 3-4 GU at three years = 151/387	Early grade 2-4 GI = 42/410 Late grade 2-4 GI at three years = 86/395	Early grade 2-4 GI = 43/410 Late grade 2-4 GI at three years = 68/387	80.5% five-year RFS (95% CI: 75.7-84.4)	77.1% five-year RFS (95% CI: 71.9-81.5)

Figure 1 - Default External Beam Radiation Therapy Fractionation used by North American genitourinary oncology expert radiation oncologists for treatment of a hypothetical patient with a favorable intermediate risk Prostate Cancer (Gleason 3+4).



PCa = prostate cancer; **hypo =** hypofractionation

Table 2 - Association between clinical practice recommendations and choice of default dose/fractionation for Gleason 3+4 prostate adenocarcinoma.

Clinical Scenario	Clinical Practice Recommendation	Conventional Fractionation (78 Gy in 2 Gy fractions, 79.2 Gy in 1.8 Gy fractions, or equivalent)	Moderate Hypofractionation (70 Gy in 2.5 Gy fractions or equivalent)	P value
Active surveillance recommendation for Gleason 6 disease	Yes	21 (91.3%)	17 (100%)	0.546
	No	2 (8.7%)	0 (0%)	
Active surveillance recommendation for Gleason 3+4 disease	Yes	3 (13.0%)	4 (23.5%)	0.607
	No	20 (87.0%)	13 (76.5%)	
SBRT for oligometastatic lesions	Yes	18 (78.3%)	12 (70.6%)	0.837
	No	5 (21.7%)	5 (29.4%)	
Treatment of pelvic lymph nodes in localized high-risk prostate cancer	Rarely	9 (39.1%)	4 (23.5%)	0.377
	Often	14 (60.9%)	13 (76.5%)	
Treatment of high-risk prostate cancer	EBRT+ADT	15 (65.2%)	7 (41.2%)	0.305
	EBRT+ADT+ brachytherapy boost	8 (34.8%)	10 (58.8%)	
Believer in advanced-imaging (Novel ligand-based PET imaging)	Yes	14 (60.9%)	14 (82.4%)	0.137
	No	9 (39.1%)	2 (11.8%)	
First choice for treatment of Gleason 6 disease who desires intervention	Brachytherapy	8 (34.8%)	12 (70.6%)	0.089
	EBRT	5 (21.7%)	1 (5.9%)	
	No preference	10 (43.5%)	4 (23.5%)	

CONFLICT OF INTEREST

None declared.

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Confidential

Advanced imaging techniques in prostate cancer

Please complete the survey below. It is 4 pages long and should take approximately 5 minutes to finish.

Thank you very much for your contribution!

Are you actively practicing clinical oncology?

◯ Yes ◯ No

Is genitourinary oncology your primary focus?

◯ Yes ◯ No

What is your specialty?

◯ Radiation oncology
◯ Medical oncology/Hematology oncology
◯ Urology
◯ None of the above

How many years has it been since you completed training (residency/oncology fellowship)?

◯ 0-4 years
◯ 5-10 years
◯ 11-20 years
◯ >20 years
◯ Still in training

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Where did you complete your training?

◯ Canada
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◯ Alaska
◯ Arizona
◯ Arkansas
◯ California
◯ Colorado
◯ Connecticut
◯ Delaware
◯ Florida
◯ Georgia
◯ Hawaii
◯ Idaho
◯ Illinois
◯ Indiana
◯ Iowa
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◯ Ohio
◯ Oklahoma
◯ Oregon
◯ Pennsylvania
◯ Rhode Island
◯ South Carolina
◯ South Dakota
◯ Tennessee
◯ Texas
◯ Utah
◯ Vermont
◯ Virginia
◯ Washington
◯ West Virginia
◯ Wisconsin
◯ Wyoming
◯ Other

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Where do you primarily practice?

◯ Canada
◯ Alabama
◯ Alaska
◯ Arizona
◯ Arkansas
◯ California
◯ Colorado
◯ Connecticut
◯ Delaware
◯ Florida
◯ Georgia
◯ Hawaii
◯ Idaho
◯ Illinois
◯ Indiana
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◯ Oklahoma
◯ Oregon
◯ Pennsylvania
◯ Rhode Island
◯ South Carolina
◯ South Dakota
◯ Tennessee
◯ Texas
◯ Utah
◯ Vermont
◯ Virginia
◯ Washington
◯ West Virginia
◯ Wisconsin
◯ Wyoming
◯ Other

How would you best describe your primary practice setting?

◯ Academic/university
◯ Hospital-based, no academic/university affiliation
◯ Free-standing, no academic/university affiliation
◯ Government employed, such as VA, military, or government-run facility
◯ Other

Confidential

How many patients with prostate cancer do you see in consultation per month on average?

◯ 0-4
◯ 5-9
◯ 10-14
◯ 15-20
◯ >20

Confidential

Please tell us more about your practice characteristics.

For this section, check all that apply.

☐ I often recommend active surveillance for patients with Gleason 6 disease.
☐ I often recommend active surveillance for patients with Gleason 3+4=7 disease.
☐ For patients with oligometastatic disease, I would consider offering stereotactic body radiation therapy to the oligometastatic lesion outside of a clinical trial.

Please select one of the following options.

◯ Most patients I see in clinic present with intact prostate for discussion of definitive treatment.
◯ Most patients I see in clinic present after prostatectomy for a discussion of adjuvant or salvage radiation.
◯ I see an even balance of patients with intact prostate and those who are post-prostatectomy.

Please select one of the following options.

◯ As a general rule for patients with high risk features, I recommend adjuvant radiation after surgery.
◯ As a general rule for patients with high risk features, I recommend observation and early salvage radiation if PSA rises.

Please select one of the following options.

◯ For localized high risk prostate cancer, I treat pelvic lymph nodes rarely.
◯ For localized high risk prostate cancer, I treat pelvic lymph nodes often.

Do you consider yourself an expert brachytherapist?

◯ Yes
◯ No

For patients with Gleason 6 disease who desire treatment, with no baseline urinary symptoms and a 40cc prostate, which would you consider your first choice for treatment?

◯ External beam radiation
◯ Brachytherapy
◯ Either external beam or brachy (no preference)

For patients with localized high risk disease, with no baseline urinary symptoms and a 40cc prostate, which would you consider your first choice for treatment?

◯ External beam radiation with ADT (androgen deprivation therapy)
◯ External beam radiation with ADT and brachytherapy boost

What is your current practice with regard to digital rectal examinations (DRE)? (Check all that apply)

☐ I routinely perform DRE before treatment
☐ I routinely perform DRE at follow-up visits
☐ I never perform DRE
☐ I believe DRE will change management
☐ I do not believe DRE will change management

What do you consider the default EBRT dose and fractionation for Gleason 3+4 prostate adenocarcinoma?

◯ Conventional fractionation: 78 Gy in 2 Gy fractions, 79.2 Gy in 1.8, or equivalent
◯ Moderate hypofractionation: 70 Gy in 2.5 Gy fractions or equivalent
◯ SBRT/Radical hypofractionation: 5-12 fractions or equivalent

Confidential

Are you aware that the NCCN recommends consideration of C-11 choline PET, but not PSMA PET for patients with prostate cancer?

◯ Yes
◯ No

The NCCN recommends considering C-11 PET in the following scenarios:

- In the setting of detectable PSA after prostatectomy
- Biochemical failure after definitive radiation
- In M0 patients on androgen deprivation therapy with a rising PSA.

What are your thoughts on these recommendations?

◯ I agree with the NCCN recommendations.
◯ The NCCN should recommend the use of C-11 PET in more scenarios than those listed above (specify)
◯ The NCCN should recommend considering C-11 PET in some, but not all of the above scenarios (specify)
◯ The NCCN should not recommend considering C-11 PET at all because there is not enough evidence to support its use in routine practice.

Please specify

_____

Do you think that the NCCN should recommend consideration of PSMA PET?

◯ The NCCN should recommend consideration of PSMA PET in the same scenarios as C-11 PET.
◯ The NCCN should recommend consideration of PSMA PET in more scenarios than C-11 PET (specify).
◯ The NCCN should recommend consideration of PSMA PET in some, but not all of the same scenarios as C-11 PET (specify).
◯ The NCCN should not recommend consideration of PSMA PET because there is not enough evidence to support its use in routine practice.

Please specify

_____

Regarding the comparison of C-11 PET to PSMA PET, select the answer which best describes your opinion.

◯ C-11 PET has better efficacy than PSMA PET.
◯ PSMA PET has better efficacy than C-11 PET.
◯ C-11 PET and PSMA PET have the same level of efficacy.
◯ There is not enough data to know whether C-11 PET or PSMA PET is more effective.

Which of the following imaging studies are available at your practice (or at an affiliated facility)?

◯ C-11 PET
◯ PSMA PET
◯ Both
◯ Neither

What is your current practice with regard to the new imaging modalities PSMA PET and C-11 PET?

◯ I routinely order them for my patients and use the results to guide treatment decision-making.
◯ I have ordered them on rare occasion for my patients and used the results to guide treatment decision-making.
◯ I do not order them, but if a patient already has results at the time I see them, I will use the results to guide treatment decision-making.
◯ I do not order them and do not use the results to guide treatment decision-making.

Confidential

What is your current practice with regard to the new imaging modalities PSMA PET and C-11 PET?

◯ I often refer patients to centers capable of performing one of these tests.
◯ On rare occasions I have referred my patients to centers capable of performing one of these tests.
◯ I do not refer them, but if a patient already has results at the time I see them, I will use the results to guide treatment decision-making.
◯ I do not refer them and do not use the results to guide treatment decision-making.

What is the primary reason you do not use results from PSMA PET or C-11 PET to guide treatment decision-making?

◯ There is not enough data to guide usage of these tests.
◯ I do not believe these tests are effective.
◯ I lack personal experience using these tests.
◯ Other (specify)

Please specify

_____

Confidential

For each of the following patient scenarios, please enter the lowest PSA value at which you would order a C-11 PET or PSMA PET. Enter 0 for "never."

Gleason 4+5=9, post-prostatectomy, consecutively rising PSA _____

Gleason 4+3=7, post-prostatectomy, consecutively rising PSA _____

Gleason 10, T3, intact prostate, pre-treatment _____

Gleason 4+3=7, T2, intact prostate, pre-treatment _____

Gleason 10, T3, post-definitive radiation _____

Gleason 4+3=7, T2, post-definitive radiation _____

In a patient with newly diagnosed cT2 Gleason 9 prostate cancer with a PSA of 200 ng/mL, who has no evidence of bone metastases by nuclear bone scan and abdominopelvic CT, which of the following would you consider for further workup?

◯ C-11 PET
◯ PSMA PET
◯ No further workup prior to therapy
◯ Other (specify)

Please specify

_____

What are the reasons you do not order PSMA PET or C-11 PET more frequently? (Check all that apply)

☐ Availability
☐ Cost
☐ Lack of evidence
☐ Unsure how to interpret
☐ Other (specify)

Please specify

_____

ORIGINAL ARTICLE

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Prostate brachytherapy with iodine-125 seeds: analysis of a single institutional cohort

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ABSTRACT

Objectives: Brachytherapy (BT) with iodine-125 seeds placement is a consolidated treatment for prostate cancer. The objective of this study was to assess the clinical outcomes in patients with prostate cancer who underwent low-dose-rate (LDR) -BT alone in a single Brazilian institution. Materials and Methods: Patients treated with iodine-125 BT were retrospectively assessed after at least 5 years of follow-up. Patients who received combination therapy (External beam radiation therapy-EBRT and BT) and salvage BT were not included.

Results: 406 men were included in the study (65.5% low-risk, 30% intermediate-risk, and 4.5% high-risk patients). After a median follow-up of 87.5 months, 61 (15.0%) patients developed biochemical recurrence. The actuarial biochemical failure-free survival (BFFS) at 5 and 10 years were 90.6% and 82.2%, respectively. A PSA nadir ≥ 1 ng / mL was associated with a higher risk of biochemical failure (HR = 5.81; 95% CI: 3.39 to 9.94; p ≤ 0.001). The actuarial metastasis-free survival (MFS) at 5 and 10 years were 98.3% and 94%, respectively. The actuarial overall survival (OS) at 5 and 10 years were 96.2% and 85.1%, respectively. Acute and late grade 2 and 3 gastrointestinal toxicities were observed in 5.6%, 0.5%, 4.6% and 0.5% of cases, respectively. For genitourinary the observed acute and late grade 2 and 3 toxicities rates were 57.3%, 3.6%, 28% and 3.1%, respectively. No grade 4 and 5 were observed.

Conclusions: BT was effective as a definitive treatment modality for prostate cancer, and its endpoints and toxicities were comparable to those of the main series in the literature.

ARTICLE INFO

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INTRODUCTION

Prostate cancer is the second most common malignant neoplasm in men (excluding nonmelanoma skin cancer), with an estimated 1 million annual diagnoses worldwide (1). There are different treatment strategies for localized disease, which include radical prostatectomy, external radiotherapy, and brachytherapy (BT) (2). Many patients can be submitted to active surveillance and treated in a timely manner (2, 3).

Brachytherapy with iodine-125 seeds placement is a consolidated treatment and yields good results over a long clinical follow-up for patients with low and selected intermediate risk prostate cancer (4, 5). Large cohorts have demonstrated

a rate of 86-87% and 79-80% of clinical control for low and intermediate risk respectively (6, 7). This modality remains the most conformal form of radiation dose delivery, allowing more effective dose escalation and good results when compared to external beam radiation therapy (EBRT) besides acceptable toxicity (2).

The objective of this study was to describe the biochemical failure-free survival (BFFS), metastasis-free survival (MFS), disease-specific survival (DSS), overall survival (OS), and treatment--related toxicities in patients with prostate cancer who underwent low-dose-rate (LDR) -BT alone in a single Brazilian institution.

MATERIALS AND METHODS

Localized prostate cancer patients treated between March 2001 and November 2010 with BT were retrospectively assessed after a minimum of 5 years of follow-up. All patients clinically candidates for BT were submitted to digital rectal examination in position of lithotomy for assessment of the procedure feasibility technique. An ultrasonography was performed for pubic arch evaluation in patients with large prostatic gland and pubic arch interference was the only technical contraindication for the implant. BT was performed with real time intraoperative planning and iodine-125 seed implants guided by transrectal ultrasonography and radioscopy. The number of seeds implanted were variable according to prostate size and planning, and the range from 73 to 122 seeds per patient were used. For all patients, the prescribed dose was 144 Gy at 90% of prostate volume. After the seeds implant, the patients were submitted to post-implant dosimetry as suggested by American College of Radiology (ACR). The dose constraints used were V100 ≤ 1cc for the rectum and V150 < 50% for the urethra. Patients who received combination therapy (EBRT and BT), salvage BT and who were lost to follow-up were excluded.

Biochemical failure was defined according to the Phoenix criteria, a rise of 2 ng / mL above nadir. The BFFS, DSS, and OS were estimated using the Kaplan-Meier method. A log-rank test and multivariable Cox regression were used to evaluate the relationship of covariates with outcomes. The incidences of acute and late gastrointestinal and genitourinary toxicities and their respective confidence intervals (95% CI) were calculated using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4 (NCI CTCAE v4.0) scoring system (8).

The level of statistical significance adopted was $p < 0.05$. Statistical analyses were performed using the Stata™ statistical program (version 13.0) (9).

RESULTS

Of the 616 patients treated with BT, 406 were included in the study. In total, 65.5% were low-risk, 30% were intermediate-risk, and 4.5% were high-risk patients. The patient's characteristics are described in Table-1.

After a median follow-up of 87.5 months, 61 (15.0%) patients developed biochemical recurrence. The actuarial BFFS at 5 and 10 years was 90.6% and 82.2%, respectively (Figure-1). There were no significant differences in the BFFS among the risk groups ($p = 0.294$) (Figure-2) and no significant associations between the BFFS and patient age, presence of comorbidities, perineural invasion, total tissue invasion, or Gleason score (Table-2). The mean PSA nadir was 0.53 ng / mL and a value ≥ 1 ng / mL was associated with a higher risk of recurrence (Figure-3A). Patients with a first PSA value (3 months after treatment) ≥ 1 ng / mL presented a higher risk of developing biochemical failure (Figure-3B). Analysis of patients whose PSA was first measured up to 60 days after BT showed that patients who had an increase in PSA after BT had a higher risk of biochemical failure than patients who presented a PSA reduction of more than 50.0% in relation to the PSA value collected before BT (HR = 2.26, 95% CI: 1.02 to 4.98); However, there was no significant difference in the risk of biochemical failure between patients who showed a reduction of less than 50.0% and those with reduction greater than 50.0%. The actuarial MFS at 5 and 10 years was 98.2% (95% CI: 96.3% to 99.1%) and 94% (95% CI: 89.9% to 96.5%), respectively. Seventeen (4.2%) patients had metastases (10 had bone metastases, 4 had visceral metastases, and 3 had lymph node metas-

Table 1 - Demographic and clinical characteristics of prostate cancer patients undergoing brachytherapy (n = 406).

	n	%
Age (years)		
< 60	113	27.8
60 - 70	156	38.4
> 70	137	33.7
Color		
White	366	92.2
Mixed	20	5.0
Yellow	6	1.5
Black	5	1.3
No information	9	
Comorbidities		
No	142	35.1
Yes	263	64.9
No information	1	
Systemic hypertension		
No	271	67.1
Yes	133	32.9
No information	2	
Cardiopathy		
No	342	84.2
Yes	64	15.8
Diabetes mellitus		
No	349	86.0
Yes	57	14.0
Hemorrhoids		
No	363	89.4
Yes	43	10.6
Gleason Score		
6	283	69.7
7 (3 + 4)	64	15.8
7 (4 + 3)	18	4.4
8	13	3.2
9	1	0.2
Perineural invasion		
No	252	87.8
Yes	35	12.2
No information	119	

Risk group+		
Low	266	65.5
Intermediate	122	30
High	18	4.4
Total percentage of tumor (%)		
< 10	153	64
10 - 19.9	69	24.7
20 - 29.9	16	6.7
30 - 39.9	7	2.9
40 - 49.9	2	0.8
≥ 50	2	0.8
No information	167	
First PSA after brachytherapy		
< 1 ng / mL	68	19
≥ 1 ng / mL	289	81
No information	49	
PSA variation after brachytherapy		
PSA rising	42	11.8
Decrease < 50%	119	33.3
Decrease ≥ 50%	196	54.9
No information	49	

+ D´Amico classification

Figure 1 - Estimates of biochemical failure-free survival in prostate cancer patients undergoing brachytherapy, obtained using the Kaplan-Meier method.

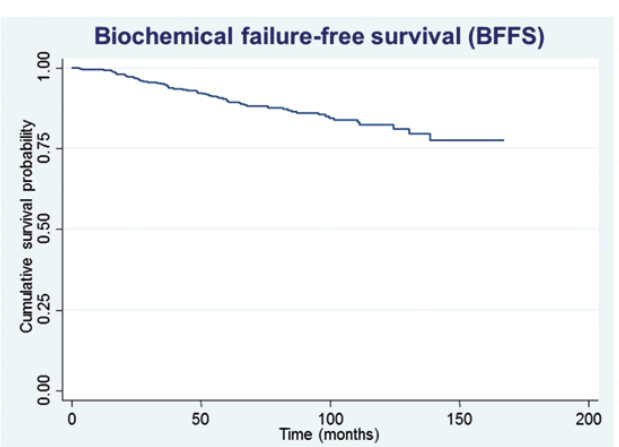


Figure 2 - Estimates of biochemical failure-free survival in prostate cancer patients undergoing brachytherapy, obtained using the Kaplan-Meier method and according to the risk group.

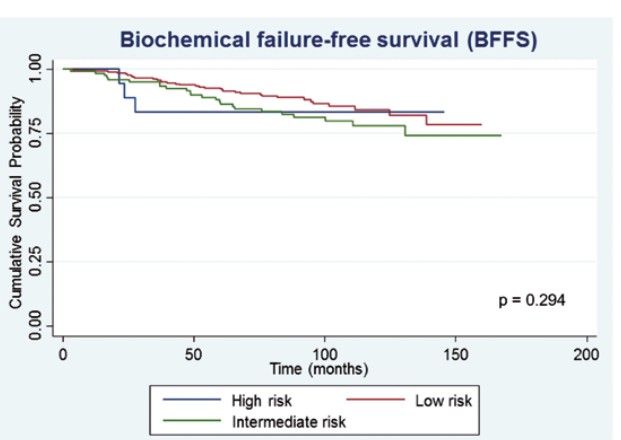


Table 2 - Univariate analysis of biochemical failure-free survival according to patient characteristics and lesions of prostate cancer patients undergoing brachytherapy (n = 406).

	Biochemical control	Mean (months) (a)	SE	HR	95% CI	p
Age (y)						0.450
< 70	87.2%	385.2	7.8	1.14	0.59-2.22	
≥ 70	83.3%	361	11.9	1.51	0.76-3.01	
Comorbidities*						0.787
No	84.5%	384.1	9.2	1		
Yes	85.1%	366.8	9.4	1.07	0.64-1.81	
Risk group+						0.294
Low	87.1%	329.3	41.6	1		
Intermediate	80.0%	380.3	8.2	1.5	0.89-2.53	
High	83.3%	379.2	7.2	1.55	0.48-5.04	
Perineural Invasion						0.133
No	88.4%	395.1	8.4	1		
Yes	76.5%	357.3	28.1	1.9	0.87-4.15	
Total % of tumor#						0.484
< 10	89.5%	390.2	12	1		
10-19.9	86.4%	297.2	22.9	1.27	0.55-2.98	
≥ 20	90.4%	374.6	13.6	1.17	0.69-1.98	
First PSA after treatment						0.019
< 1 ng / mL	94.0%	389.7	9.6	1		
≥ 1 ng / mL	83.0%	370.4	8.6	2.85	1.03-7.90	
PSA Nadir						≤ 0.001
< 1 ng / mL	90.3%	397.4	6.5	1		
≥ 1 ng / mL	59.3%	294.9	19.9	5.81	3.39-9.94	
Gleason score						0.795
6	85.5%	379.6	8.2	1		
7 (3 + 4)	82.3%	351.5	14.4	1.09	0.56-2.12	
7 (4 + 3)	86.4%	383.6	33.8	0.89	0.38-2.10	
8 or 9	78.6%	321	6.7	1.83	0.57-5.91	

(a) = BFFS mean time; **SE =** Standard error; ***** = Comorbidities: Systemic hypertension, cardiopathy, diabetes mellitus; **+ =** D´Amico classification; **# =** Proportion: Adenocarcinoma / normal prostate tissue; **HR =** Hazard Ratio; **CI =** Confidence Interval; **p =** p Value of Log-Rank test

Figure 3A - Estimates of biochemical failure-free survival in prostate cancer patients undergoing brachytherapy, obtained using the Kaplan-Meier method and according to the PSA nadir.

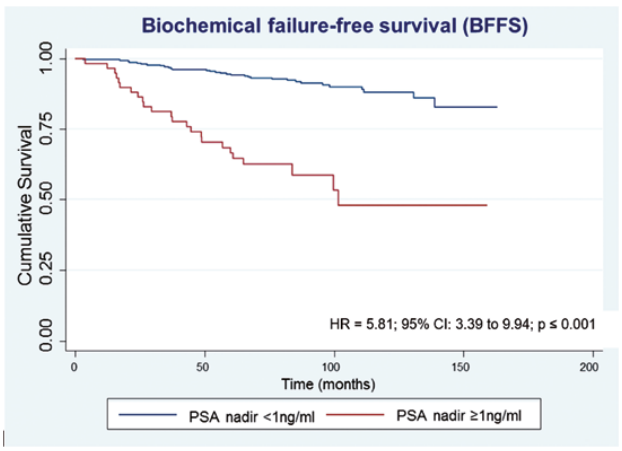


Figure 3B - Estimates of biochemical failure-free survival in prostate cancer patients undergoing brachytherapy, obtained using the Kaplan-Meier method and according to the first PSA.

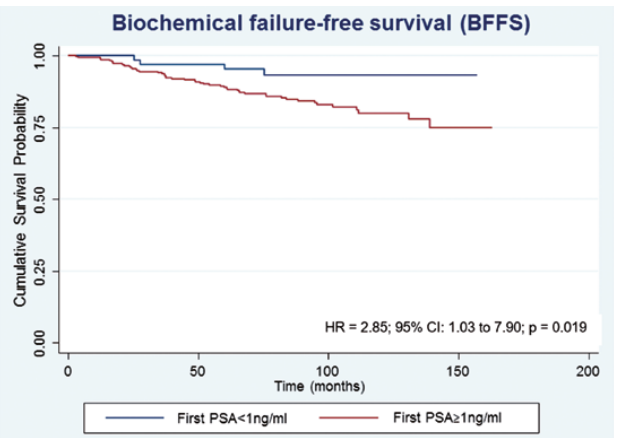
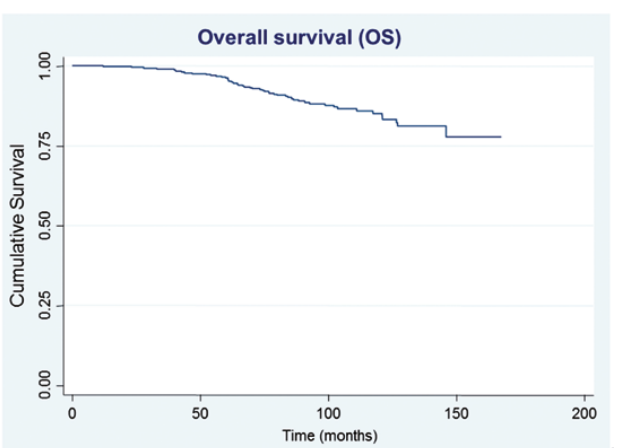


Figure 4 - Estimates of overall survival in prostate cancer patients undergoing brachytherapy, obtained using the Kaplan-Meier method.



tases), 7 of whom died. Three patients (0.3%) died from prostate cancer and 4 died from cardiovascular causes during the follow-up. The actuarial OS at 5 and 10 years was 96.2% and 85.1%, respectively (Figure-4).

Acute grade ≥ 2 and grade ≥ 3 gastrointestinal toxicities were observed in 5.6% and 0.5% of the cases, respectively. Late grade ≥ 2 and grade ≥ 3 gastrointestinal toxicities were observed in 4.6% and 0.5% of the cases, respectively. There were no significant associations between age, diabetes mellitus, cardiopathy, hemorrhoids, neoadjuvant hormone therapy, prostate volume, and incidence of acute and late gastrointestinal toxicity.

The acute grade ≥ 2 and grade ≥ 3 genitourinary toxicity incidences were 57.3% and 3.6%, respectively. Late grade ≥ 2 and grade ≥ 3 symptoms were observed in 28% and 3.1% of patients, respectively. There were no significant associations between age, diabetes mellitus, cardiopathy, hemorrhoids, neoadjuvant hormone therapy, prostate volume, and incidence of genitourinary toxicity. Patients who had acute urinary retention had a greater prostate volume (median = 47.0 cm^3, p_{25}: 29.0 cm^3; p_{75}: 59.4 cm^3) than those who did not have these features (median = 37.0 cm^3; p_{25}: 29.0 cm^3; p_{75}: 46.7 cm^3) (p = 0.017).

Patients with a baseline International Prostate Symptom Score (IPSS) of greater than 10 were at an increased risk of acute genitourinary toxicity ≥ 2 (RR = 1.40, 95% CI: 1.16 to 1.69) (p = 0.004) and late genitourinary toxicity ≥ 2 (RR = 1.79; 95% CI: 1.26 to 2.56) (p = 0.005) (Tables 3 and 4).

DISCUSSION

Prostate cancer is diagnosed at progressively earlier stages and the proportion of men with low-

Table 3 - Characteristics associated with incidence of acute genitourinary toxicity ≥ 2 in prostate cancer patients undergoing brachytherapy (n = 393).

	Acute genitourinary toxicity ≥ 2				RR	95% CI		p
	No		Yes					
	(n = 168)		(n = 225)					
	n	%	n	%				
Age group (years)								0.924
< 60	39	41.0	56	59.0	1			
60 - 70	74	43.0	98	57.0	0.97	0.78	1.19	
> 70	55	43.7	71	56.4	0.96	0.96	1.20	
Diabetes mellitus								0.305
No	141	41.7	197	58.3	1			
Yes	27	49.1	28	50.9	0.87	0.66	1.15	
Cardiopathy								0.173
No	138	41.3	196	58.7	1			
Yes	30	50.9	29	49.1	0.84	0.64	1.10	
Neoadjuvant hormone therapy								0.119
No	135	41.0	194	59.0	1			
Yes	33	51.6	31	48.4	0.82	0.63	1.07	
IPSS								0.004
< 10	111	47.8	121	52.2	1			
10 - 20	19	27.1	51	72.9	1.40	1.16	1.69	
> 20	2	22.2	7	77.8	1.49	1.02	2.16	
Risk group								0.336
Low	118	45.4	142	54.6	1			
Intermediate	44	37.6	73	62.4	1.14	0.95	1.37	
High	6	37.5	10	62.5	1.14	0.77	1.70	

RR = Relative risk; **IPSS =** International Prostate Symptom Score; **CI =** Confidence Interval; **p =** p Value of X^2

-risk disease is increasing (10). The approach to low--risk prostate cancer involves active surveillance (11) or treatment with radical prostatectomy, external radiation therapy, or BT (2). Mostly, there are several published series comparing all treatment modalities, once data from prospective studies are not broadly available. Prostate BT has the same efficacy as other radical treatments on localized disease (6, 12-14).

Grimm et al. (7) published a series of 125 cases of prostate BT with iodine-125 seed implants. After 10 years of follow-up, a BFFS of 85.1% was achieved, and in low-risk patients, the rate was 87%. Kollmeier et al. (15) published an institutional experience with prostatic iodine-125 and palladium-103 implants after a minimum follow-up of 5 years. In total, 336 patients with localized disease were treated, and a BFFS of 77% was obtained. Disease-related factors, including the initial PSA level, Gleason score, and stage, were significant predictors of biochemical failure.

The present study demonstrated PSA control rates similar to those in the literature. The majority of patients treated in this cohort were low--risk and no statistically significant difference in outcomes among the risk groups were observed probably due to the poor representation of intermediate and high-risk patients.

Biochemical control rates demonstrated in

Table 4 - Characteristics associated with incidence of late genitourinary toxicity ≥ 2 in prostate cancer patients undergoing brachytherapy (n = 390).

	Late genitourinary toxicity ≥ 2				RR	95% CI		p
	No		Yes					
	(n = 281)		(n = 109)					
	n	%	n	%				
Age group (years)								0.231
< 60	64	67.4	31	32.6	1			
60 - 70	132	76.3	41	23.7	0.73	0.49	1.08	
> 70	85	69.7	37	30.3	0.93	0.63	1.38	
Diabetes mellitus								0.281
No	244	73.0	90	27.0	1			
Yes	37	66.1	19	33.9	1.26	0.83	1.89	
Cardiopathy								0.483
No	237	71.4	95	28.6	1			
Yes	44	75.9	14	24.1	0.84	0.52	1.38	
Neoadjuvant hormone therapy								0.606
No	238	72.6	90	27.4	1			
Yes	43	69.4	19	30.6	1.12	0.74	1.69	
IPSS								0.005
< 10	175	76.1	55	23.9	1			
10 - 20	40	57.1	30	42.9	1.79	1.26	2.56	
> 20	5	55.6	4	44.4	1.86	0.86	4.00	
Risk group								0.092
Low	195	75.6	63	24.4	1			
Intermediate	76	65.5	40	34.5	1.41	1.01	1.96	
High	10	62.5	6	37.5	1.54	0.79	2.99	

RR = Relative risk; **IPSS =** International Prostate Symptom Score; **CI =** Confidence Interval; **p =** p Value of X^2

this study can also be compared to the main series of dose escalation EBRT. The same institution reported outcomes of high dose EBRT with Intensity Modulation Radiation Therapy (IMRT) and the biochemical control rate was 86.4% after a median follow-up of 58 months. Five year BFFS was 91.7% for low risk patients (16).

A positive aspect of our cohort is that all patients were submitted to post-implant dosimetry. It is well know that an adequate prostate coverage with the prescription dose in the post-implant analysis is related to better BFFS (17). Pereira da Ponte Amadei et al. (18) published a retrospective data of first patients treated at the same hospi-

tal without post-implant dosimetry, and the BFFS rate was lower (80% of 5-year BFFS).

Variables related to clinical outcomes were also identified in this study. In our institutional experience, nPSA < 1 ng / mL was related to better chance of biochemical control with IMRT (19) and these findings were confirmed in the present BT cohort. Furthermore, patients who had this PSA value in the first measure after the procedure also have a better prognosis. Several studies have analyzed PSA dynamics after prostate cancer treatment with radiotherapy (20, 21). Ko et al. (22) associated nPSA < 0.5 ng / mL with a higher BFFS; in addition, those who achieved this value in the first 5 years after the procedure showed an even higher BFFS than those who achieved it after 5 years.

Data regarding the treatment-related toxicity were also collected in the present study. It is known that BT-related toxicity and its impact on quality of life are comparable to those of other treatment methods (5, 23, 24). There are several factors relating to greater morbidity in prostate BT, including IPSS, prior transurethral resection, large (> 60 cm^3) or small (< 20 cm^3) glands, acute prostatitis, and inflammatory bowel disease (25).

Our genitourinary toxicity results had comparable or lower rates in relation to the main series reporting these data (26, 27). It is known that prostate size is not necessarily a limiting factor in regard to undergoing treatment (28). In a series of 325 men treated with iodine-125 implants, Stone and Stock (29) did not notice a significant difference in urinary symptoms of patients with large and small prostates. However, our study demonstrated a relationship between acute urinary retention and prostate volume; therefore, patients with larger prostate volume have higher risk of acute urinary retention. Our gastrointestinal toxicity data were also quite encouraging and comparable to those of large prostate BT centers (30, 31). The BT-related toxicity may also be compared to EBRT. This analysis was performed in previous studies (14) and the conclusions are, in general, BT is associated with higher rates of acute urinary toxicities, mainly related to obstructive symptoms and urinary retention. Moreover, BT is related to lower rates of acute and late gastrointestinal toxicities. These aspects are consistent with our institutional data (16).

To the best of our knowledge, the present study represents the largest cohort with a long term follow-up of patients submitted to low dose BT in Brazil and Latin America and had showed satisfactory results. Although BT has been used less often in recent years in the US (32), it remains the most conformal form of radiation delivery as well as the optimal means for dose-escalation. Besides that, it is a quick, low-risk surgical procedure performed in a single day and a quick recovery for the patients. These characteristics are interesting for developing countries with poor installed capacity for radiation therapy institutions (33).

CONCLUSIONS

BT with iodine-125 was effective at this institution as a definitive treatment modality for prostate cancer, and its endpoints and toxicities were comparable to those of the main series in the literature. Well-screened patients with low- and intermediate-risk prostate cancer should be offered this procedure as often as other therapeutic options, such as external radiotherapy and radical prostatectomy.

ABBREVIATIONS

RP = radical prostatectomy
BT = brachytherapy
EBRT = external beam radiation therapy
BFFS = biochemical failure-free survival
MFS = metastasis-free survival
DSS = disease-specific survival
OS = overall survival
LDR = low-dose-rate
HR = hazard ratio
p = p value
NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events
PSA = prostate-specific antigen
IPSS = International Prostate Symptom Score
nPSA = PSA nadir value

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Small cell bladder cancer: should we consider prophylactic cranial irradiation?

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ABSTRACT

Purpose: To describe the clinical characteristics, treatment patterns, and outcomes in patients with small cell bladder cancer at our institution, including those who received prophylactic cranial irradiation (PCI) for the prevention of intracranial recurrence.
Materials and Methods: Patients with small cell bladder cancer treated at a single institution between January 1990 and August 2015 were identified and analyzed retrospectively for demographics, tumor stage, treatment, and overall survival.
Results: Of 44 patients diagnosed with small cell bladder cancer, 11 (25%) had metastatic disease at the time of presentation. Treatment included systemic chemotherapy (70%), radical surgery (59%), and local radiation (39%). Six patients (14%) received PCI. Median overall survival was 10 months (IQR 4 - 41). Patients with extensive disease had worse overall survival than those with organ confined disease (8 months vs. 36 months, respectively, p = 0.04). Among those who received PCI, 33% achieved 5 - year survival.
Conclusion: Outcomes for patients with small cell bladder cancer remain poor. Further research is indicated to determine if PCI increases overall survival in small call bladder cancer patients, especially those with extensive disease who respond to chemotherapy.

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Prophylactic Surgical Procedures; Urinary Bladder Neoplasms; Carcinoma, Small Cell

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INTRODUCTION

Small cell carcinoma of the bladder is a rare, biologically aggressive neuroendocrine cancer that is locally destructive and disseminates early. Due to the high risk of systemic relapse following surgical resection alone, platinum - based chemotherapy is recommended in the neoadjuvant setting followed by consolidation surgery and /or radiation in those who respond (1, 2). Despite this aggressive approach, outcomes remain poor (3).

There has been growing enthusiasm for prophylactic cranial irradiation (PCI) for those patients who demonstrate a response to initial chemotherapy to decrease the risk of intracranial metastases. Although evidence for this approach is limited in small cell bladder cancer, there is strong evidence supporting its use in patients with small cell lung cancer, 40 - 80% of whom develop brain metastases within 2 years of diagnosis (4-6). Use of PCI in limited stage small cell lung cancer has been well established since the early 1990s. A meta-analysis by Auperin et al. showed a 5.4 percent increase in the rate of survival at three years (5). Phase III studies have also demonstrated that PCI improves overall survival from 13% to 27% in those with extensive stage small cell lung

cancer at 1 - year (7). As a result, PCI has become a standard of care in some patients with small cell cancer of the lung. However, it is unclear if the same survival benefit of PCI extends to patients with extrapulmonary small cell carcinoma, where the reported incidence of brain metastases is only 5 - 18% (2, 8, 9).

For this reason, we reviewed our institutional experience with small cell carcinoma of the bladder, including a series of patients who received PCI to investigate its use in this population.

MATERIALS AND METHODS

Study Population

Using a Boolean search (keyword - based text search using logical operators such as AND, OR, NOT) of surgical pathology reports within the electronic medical record, we identified patients diagnosed with small cell bladder carcinoma at our institution between January 1990 and August 2015. All patients had confirmed histological diagnosis of small cell cancer of the bladder established by a trained genitourinary pathologist. We further identified patients who received PCI. The decision to proceed with PCI was made at the discretion of the patient's treating physician.

Outcomes

Patient demographics, stage at presentation, treatment, and outcomes, including intracranial relapse rates and overall survival, were evaluated upon retrospective review of the electronic medical record. Overall survival was recorded from the date of histological diagnosis. Dates of death were obtained from the medical record and a search of the public death records.

The incidence of intracranial relapse was defined by development of a cranial metastasis during the study period. Overall survival was stratified by limited and extensive disease, with limited disease defined as organ confined malignancy (stage T2 or less, N0, M0) and extensive disease defined as stage T3 or greater, or N1, or M1 or greater.

Statistical analysis

Descriptive statistics were performed by calculating frequencies of categorical variables and the median and interquartile range (IQR) for continuous variables. Intracranial relapse was compared between those patients who did and did not receive PCI using a chi - square test. Overall survival was compared between patients with localized and extensive disease using a Mann Whitney U test. Analyses were performed using SPSS software, version 20 (IBM Corp., Armonk, NY). Statistical significance was defined as $p < 0.05$ using two - tailed tests. The University of Pittsburgh institutional review board approved the study (PRO15090222).

RESULTS

Characteristics of the study population are summarized in Tables 1 and 2. Of 44 patients included in the study, 73% were male, and the median age at diagnosis was 77 years (IRQ 67 - 80). One third (33%) were smokers at the time of diagnosis. Only 2 patients (5%) had pure small cell carcinoma, whereas the majority (95%) had mixed histology (a predominance of small cell carcinoma mixed with urothelial carcinoma). One in four (25%) presented with metastasis; forty patients (91%) had stage T2 disease or greater at the time of diagnosis.

Overall, there was a 10.2 - month median overall survival (IQR 4 - 41) and a 16% 5 - year survival. The majority received multimodal therapy, as 59% were treated with radical surgery, 39% with local radiation, 70% with systemic chemotherapy, and 14% with PCI. When analyzed separately, patients with extensive disease had an overall survival of 8 months (IQR 3 - 35) versus 36 months (IRQ 8 - 64) in those with limited disease ($p = 0.04$). In total, 4 (9%) patients developed brain metastases.

Specific details of care and outcomes of patients who received PCI can be found in Table-3. In the subset of patients treated with PCI, 50% had extensive disease at presentation and there was a 33% 5 - year survival and a median overall survival of 30 months (IQR 6 - 100). One of these six patients (17%) experienced intracranial relapse.

Table 1 - Characteristics of study population.

Characteristics	n=44
Age at Diagnosis, years, (IQR)	77 (67-80)
Gender (%)	
Male	32 (73)
Female	12(27)
Smoker (%)	33 (75)
T Stage (%)	
Tis	1 (2)
T1	3 (7)
T2	19 (43)
T3	13 (30)
T4	8 (18)
N Stage (%)	
N0/NX	35 (80)
N1	5 (11)
N2/N3	4 (9)
Metastases at Diagnosis (%)	11 (25)
Radical Surgery (%)	26 (59)
Cystectomy (Ileal Conduit)	18 (41)
Cystectomy (Neobladder)	5 (11)
Aborted Cystectomy	1 (2)
Partial Cystectomy	1 (2)
Local Radiation (%)	17 (39)
Prophylactic Cranial Irradiation (%)	6 (14)
Systemic Chemotherapy (%)	31 (70)
Neoadjuvant	12 (27)
Adjuvant	16 (36)
Both	3 (7)
1-Year Survival (%)	23 (52)
5-Year Survival (%)	7 (16)
Overall Survival, median, months (IQR)	10 (IQR 4-41)

IQR = interquartile range

Table 2 - Characteristics of patients treated with prophylactic cranial irradiation.

Characteristic	n=6
Age at Diagnosis, years, (IQR)	77 (67-80)
Gender (%)	
Male	6 (100)
Smoker (%)	6 (100)
T Stage (%)	
Tis	1 (17)
T1	0
T2	3 (50)
T3	2 (33)
T4	0
N Stage (%)	
N0/NX	5 (83)
N1	1 (17)
N2/N3	0
Metastases at Diagnosis (%)	2 (33)
Radical Surgery (%)	2 (33)
Cystectomy (Ileal Conduit)	1 (17)
Cystectomy (Neobladder)	1 (17)
Local Radiation (%)	4 (67)
Systemic Chemotherapy (%)	5 (83)
Neoadjuvant	2 (33)
Adjuvant	2 (33)
Both	1 (17)
1-Year Survival (%)	4 (67)
5-Year Survival (%)	2 (33)
Overall Survival, median, months (IQR)	30 (IQR 6-100)

DISCUSSION

Small cell carcinomas of the bladder are aggressive malignancies with a high propensity for early metastasis. In our study, 25% had metastasis at the time of diagnosis and > 90% presented with stage T2 or higher, consistent with prior observational studies (3). Accordingly, 70% of patients were treated with local surgery or radiation combined with systemic chemotherapy and 14% of patients were treated with PCI. The median overall survival was 10 months and the 5 - year survival was 16%. Among those who received PCI, 5 - year survival was 33%.

For many patients with small cell lung cancer, PCI is recommended for prevention of intracranial relapse. Several randomized controlled trials show that PCI decreases brain metastases

Table 3 - Disease details and outcomes of patients treated with prophylactic cranial irradiation.

Patient	Agee	Metastasis at Diagnosis	TMN Stage	Pre-Treatment MRI or CTH	Surgery	Type	Chemotherapy	Type	Response to Chemotherapy	Local Radiation	Cranial relapse	Extra Cranial Relapse	Local Recurrence	Survival (mths)
1	79	Yes	T2bNxMx	MRI	Yes	TURBT	Yes	Neo	Yes	Yes	No	Yes	Yes	23.8
2	75	No	T3bN1Mx	MRI	Yes	CxIC	Yes	Neo	Yes	No	No	Yes	Yes	6.5
3	72	Yes	T3NxMx	MRI	Yes	TURBT	Yes	Adjuv	Yes	Yes	Yes	Yes	Yes	4.2
4	70	No	TisN0Mx	MRI	Yes	CxNB	Yes	Neo	Yes	No	No	No	No	77.7
5	78	No	T2NxMx	CTH	Yes	TURBT	Yes	Adjuv	Limited	Yes	No	Yes	Yes	36.3
6	49	No	T2NxMx	CTH	Yes	TURBT	Yes	Neo	Yes	Yes	No	No	Yes	166.4

All patients were male and had a smoking history

Adjuv = Adjuvant Chemotherapy; **CTH =** Computerize Tomography of the Head; **MRI =** Magnetic Resonance Imaging of the Head; **Neo =** Neoadjuvant Chemotherapy; **CxIC =** Radical Cystectomy with Ileal Conduit Diversion; **CxNB =** Radical Cystectomy with Neobladder Diversion

and increases overall survival in patients with both limited - and extensive - stage small cell lung cancer in those who have a good response to initial chemotherapy (5, 7, 10), with an overall increase in survival at 1 - year from 13 to 27% (7). Meta - analyses have shown a significant decrease in the incidence of brain metastases with a hazard ratio (HR) of 0.48 (95% confidence interval [CI] 0.39 - 0.60) (11), and a decrease in overall mortality by 4.4% in patients treated with PCI (4). Of note, there is one contemporary randomized control trial, which questions the utility of PCI in those with extensive disease; in that trial, there was no survival benefit between groups (12).

It remains unclear if the benefits of PCI in small cell lung cancer can be extrapolated to patients with small cell bladder cancer. Few of the published studies discussing PCI in extrapulmonary small cell have included primary bladder tumors, (8, 13-17) the largest documented series citing only 3 patients (2). Most have discouraged the use of PCI in this population as the incidence of brain metastases is thought to be as low as 5 - 18% (2, 8, 9). A pooled - analysis of prior studies (15) concluded that the incidence of brain metastases was 10.5% (95% confidence interval [CI] 7.5% to 14.1%), which is similar to the findings in our series (9%). However, the risk of brain metastases in small cell bladder cancer patients with extensive disease at presentation (bulky tumors, advanced stage (> T3a), or non - cerebral metastasis) increases to 50% (18). Therefore, patients with extensive disease and a good clinical response to chemotherapy may benefit most from PCI. While further study is needed, the Canadian Association of Genitourinary Oncologist guidelines recommend offering PCI in this group, due to the significant negative impact on quality of life and poor survival following development of cranial metastasis (19).

While PCI may improve functioning by preventing or delaying brain metastasis, there are known side effects. Neurocognitive toxicities may preclude its use in patients where the benefit of the treatment is less clear. Acute toxicities are generally mild and include anorexia, constipation, headaches, and leg weakness. A study by Slotman et al. showed hair loss and fatigue were higher in patients who received PCI, while there was no difference in emotional functioning (20). In early

treatment techniques, there were significant neurologic sequelae. However, contemporary PCI has fewer long - term effects and the clinical significance of these effects is unclear. Old age (> 60), concurrent administration with chemotherapy, and high radiation doses have all been associated with the neurotoxicity of PCI (21-23). While self - reported decline of cognitive functioning has been reported (24), a number of prospective randomized control trials in the 1990s showed no clinically significant long - term neurocognitive effects in PCI patients (25, 26). Moreover, baseline neurocognitive function may be impaired prior to PCI in small cell cancer patients, further complicating this research (23). Methods to reduce neurotoxicity are underway, including hippocampal avoidance, which has resulted in durable in - brain control and an absence of neurocognitive decline (27, 28).

The findings of this study must be considered in the context of several limitations. Given the rarity of this disease, our series is limited to a small number of patients. However, our experience adds to the current body of literature describing this rare condition and, to our knowledge, includes the largest series of patients treated with PCI. Second, we did not have a method to study cognitive or quality - of - life effects of PCI in our cohort and therefore cannot comment on the tolerability or side effects of this treatment. Third, patients were primarily male and treated at a large academic medical center. Therefore, these results may not be generalizable to other populations. Lastly, not all patients in the study had baseline MRIs. Thus, some patients may have had occult brain metastasis at the time of presentation and may be incorrectly categorized.

Though the benefits of PCI in patients with extrapulmonary small cell carcinoma have been questioned, there may be benefit in select patients, particularly those who present with extensive disease and a high risk of brain metastasis who show an initial response to chemotherapy. Further study is warranted to examine both the benefits and neurocognitive risks of PCI in this population.

CONCLUSIONS

PCI is now standard of care in some small cell lung cancer patient populations where it has been shown to increase overall survival. We present the largest documented cohort of small cell bladder cancer patients who were treated with PCI. Further research is indicated to determine if PCI may also increase overall survival in small call bladder cancer patients, especially those with extensive disease who have a response to chemotherapy.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Moderate or severe LUTS is associated with increased recurrence of non – muscle – invasive urothelial carcinoma of the bladder

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ABSTRACT

Purpose: Non - muscle - invasive bladder cancer (NMIBC) can recur despite transurethral resection (TURBT) and adjuvant intravesical therapy. Tobacco products excreted in the urine are hypothesized to cause tumor - promoting effects on urothelial cells through direct contact. We determined if moderate or severe lower urinary tract symptoms (LUTS) (defined as International Prostate Symptom Score [IPSS] ≥ 8) was associated with increased tumor recurrence.

Materials and Methods: We retrospectively identified 70 consecutive men initially diagnosed with NMIBC at our institution from 2010 - 2016. Means were compared with independent T - test and proportions with chi - square analysis. Multivariate logistic regression was performed to determine independent predictors of recurrence.

Results: The majority of patients had Ta disease (58.6%) followed by T1 (28.6%) and Tis (12.9%). Forty - one (58.6%) patients had moderate or severe LUTS upon presentation within 30 days of initial TURBT with mean IPSS of 13.2 vs. 5.2 in the control group ($p < 0.01$). Biopsy - proven tumor recurrence occurred in 24 (34.3%) patients at mean follow-up of 31.7 months. Mean time to recurrence was 14.6 months. Moderate or severe LUTS was an independent predictor of tumor recurrence (odds ratio [OR]: 19.1, 95% confidence interval [CI]: 2.86 - 127; $p = 0.002$). Voiding or storage symptoms based on the IPSS did not independently correlate with tumor recurrence ($p = 0.08$ and $p = 0.31$, respectively) although total mean IPSS score did (OR: 1.26, 95% CI: 1.07 - 1.47, $p = 0.005$).

Conclusions: The presence of moderate or severe LUTS may be an important prognostic factor in NMIBC. Patients with significant urinary symptoms could be monitored more aggressively due to higher recurrence risk.

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INTRODUCTION

Approximately 75% of bladder cancer patients present with non - muscle invasive disease classified as Ta (mucosa only), T1 (lamina propria invasion), or carcinoma in situ (CIS) (1, 2). Non - muscle invasive bladder cancer (NMIBC) has a high rate of recurrence and progression despite local treatment (3). Recurrence rates range from < 20% for low - grade, Ta lesions to 80% for high - grade, T1 tumors (4). Probabilities for recurrence are dependent on tumor size, grade, stage,

multiplicity, and initial response to intravesical therapy (5).

Risk factors for urothelial carcinoma (UC) include tobacco abuse, which is estimated to account for 50% of tumors (6). It is hypothesized that tobacco products exert a tumor - promoting effect on the urothelial cells of the bladder mucosa through direct contact with the urine via mechanisms such as immunomodulation (7).

Benign prostatic hypertrophy (BPH) is common in men and can cause bladder outlet obstruction (BOO), which can result in lower urinary tract symptoms (LUTS) such as frequency, urgency, and hesitancy (8). Retained urine secondary to BPH - related LUTS can theoretically lead to increased exposure to urinary carcinogens and higher recurrence rates. In this study, we determined if moderate or severely symptomatic LUTS at the time of diagnosis was associated with greater tumor recurrence in male patients being treated for NMIBC.

MATERIALS AND METHODS

Data Collection

After institutional review board approval, we retrospectively identified 70 male patients with newly - diagnosed NMIBC at our institution between January 2010 and December 2016. Pathology was confirmed by central histopathological review. We excluded patients with non - pure urothelial carcinoma of the bladder, muscle - invasive or metastatic disease (confirmed through pathology or radiographic imaging), prior history of urothelial carcinoma of the urinary tract, or concurrent or prior tumors outside of the bladder (upper tracts, prostate, urethra). Patients re - staged to muscle - invasive disease after repeat transurethral resection (TURBT) were not included.

Socio - demographics and comorbidity indicators (Charlson Comorbidity Index [CCI]) were abstracted from the initial Urology clinic visit. International Prostate Symptom Score (IPSS), a standardized, validated screening tool to self - report bothersome urinary symptoms, was completed by all patients at the initial visit. IPSS consisted of seven questions regarding urinary bother, which were subcategorized into questions dealing with voiding symptoms (incomplete emptying, intermittency, weak stream, and straining to void) and those dealing with storage symptoms (frequency, urgency, and nocturia), as well as an overall quality of life (QoL) score. Moderate or severe LUTS was defined as an IPSS ≥ 8. American Society of Anesthesiologists (ASA) score was assessed at time of TURBT, and follow-up was defined from time of initial TURBT until date of last contact or death. Tumor size was estimated based on the area of resection from the operative note, and for multifocal tumors, the size of the largest lesion treated was used. Pathological stage and grade of the most aggressive tumor on initial or re - resection TURBT was assigned with CIS considered to be the most aggressive stage for NMIBC.

Clinical management and follow-up

Patients were treated according to NCCN bladder cancer guidelines for NMIBC (9). Baseline upper tract imaging was performed on all patients with CT urogram, non - contrast CT scan, or renal ultrasound and bilateral retrograde pyelograms in the presence of renal dysfunction. Initial TURBT was completed within 60 days of presentation to the Urology clinic, and bladder tumors were completed resected on initial or repeat TURBT based on subjective intraoperative review. Utilization of post - resection mitomycin C was variable, but patients with incomplete initial TURBT, high - grade bladder tumors, or T1 tumors (with or without muscularis propria present in the initial specimen) underwent re - resection within 4 - 6 weeks for accurate staging. Ureteral washings, prostatic urethral biopsies, or random bladder biopsies were not routinely performed at the time of initial or repeat TURBT, and blue light cystoscopy was not available, so all procedures were done under white light.

Patients with low - grade, Ta bladder tumors were not routinely treated with adjuvant intravesical chemotherapy and were followed with observation. Patients with high - grade, T1, or CIS tumors, however, received at least one six - week induction cycle of adjuvant intravesical Bacillus Calmette - Guérin (BCG) 2 - 4 weeks after initial or repeat TURBT.

Follow-up after TURBT and adjuvant intravesical therapy (if indicated) consisted of clinic cystoscopy and urine cytology every 3 months for the first year, every 6 months for the second year, and annually thereafter indefinitely. Upper tract imaging was performed every 1 - 2 years. We did not routinely perform biopsies after adjuvant intravesical therapy to assess for tumor response unless a clinical suspicion for recurrence arose based on clinic cystoscopy, urine cytology, upper tract imaging, or new - onset gross hematuria. Recurrence was based on definitive diagnosis from histopathology from repeat TURBT or biopsy of the urinary tract during the surveillance period.

Statistical Analysis

Sociodemographic, comorbidity, and other relevant clinical variables were compared between patients based on severity of LUTS and our primary endpoint, which was the development of a pathology - proven recurrence in the urinary tract during follow-up. Continuous variables were reported as means and standard deviations (SD) and categorical variables as frequency counts and percentages. We used the independent T - test to determine any differences in continuous variables and the chi - square test for categorical variables. Multivariate logistic regression analysis was performed to evaluate the association of recorded variables with our primary endpoint, and odds ratios (OR) were reported. Factors analyzed included any variable with a statistically significant association with our primary endpoint on bivariate analysis. Statistical analysis were performed with the Statistical Package for the Social Sciences (SPSS) software package (IBM Corporation, Armonk, NY). All tests were 2 - sided, with $p < 0.05$ considered to be statistically significant.

RESULTS

The majority of patients had small (< 2.0 cm) (54.3%), solitary (61.4%) tumors and did not receive post - resection mitomycin C (75.7%). Ta disease was the most predominant (58.6%) followed by T1 (28.6%) and Tis (12.9%), and the majority of tumors were high - grade (55.7%).

Moderate or severe LUTS was seen in 41 (58.6%) men upon presentation to the Urology clinic within 30 days of initial TURBT. These patients had a mean IPSS of 13.2 compared to 5.2 in those with mild LUTS ($p < 0.01$). Patients with moderate or severe LUTS were more likely to be older (mean age: 69.2 vs. 59.5 years, $p < 0.01$), on BPH medications (78% vs. 17.2%, $p < 0.01$), and have high - grade tumors (70.7% vs. 34.5%, $p = 0.003$) (Table-1). The most common class of BPH medications taken by our study population were alpha - blockers (n = 24; 64.9%) followed by 5 - alpha - reductase inhibitors (n = 11; 29.7%) and phosphodiesterse - 5 inhibitors (n = 2; 5.4%).

Twenty - four patients (34.3%) experienced a pathology - proven recurrence in the urinary tract. Mean follow-up was 31.7 months, and mean time to first recurrence was 14.6 months. Three patients (4.3%) had a recurrence on their first surveillance cystoscopy at 3 months. The majority of recurrences were within the urinary bladder (n = 23) with one occurring superficially in the prostatic urethra. Twenty - two of 41 (53.7%) patients with moderate or severe LUTS developed a tumor recurrence during follow - up versus 2 of 29 (6.9%) with mild LUTS (Table-1). Tumor progression occurred in four patients with three having pathological tumor upstaging and one developing muscle - invasive disease.

Patients who experienced a recurrence had higher overall urinary bother (mean IPSS: 13.3 vs. 8.2, $p < 0.01$) including more voiding symptoms (mean IPSS voiding: 7.9 vs. 5.0, $p < 0.01$) and storage symptoms (mean IPSS storage: 5.4 vs. 3.2, $p < 0.01$), and worse urinary QoL (mean IPSS QoL: 3.8 vs. 2.5, $p < 0.01$) (Table-2). These patients also had more high - grade tumors (79.2% vs. 43.5%, $p = 0.004$) and advanced tumor stage ($p = 0.001$) (Table-2).

On multivariate analysis, the presence of moderate or severe LUTS was an independent predictor of tumor recurrence (OR: 19.1, 95% confidence interval [CI]: 2.86 - 127; $p = 0.002$) in addition to pathological tumor stage ($p < 0.05$) (Table-3). Voiding or storage symptoms based on the IPSS did not independently correlate with tumor recurrence in our multivariate model ($p = 0.08$ and $p = 0.31$, respectively) (Table-4) although

Table 1 - Patient characteristics and outcomes based on the degree of LUTS.

	Mild LUTS [IPSS < 8] (n = 29)	Moderate or severe LUTS [IPSS > 8] (n = 41)	Total (n = 70)	p - value
Sociodemographic and clinical characteristics				
Mean age, years (SD)	59.5 (10.9)	69.2 (10.5)	65.2 (11.6)	< 0.01
Mean BMI, kg / m2 (SD)	30.7 (7.4)	29.1 (6.3)	29.8 (6.8)	0.35
Race, no. (%)				**0.34**
White	23 (79.3)	36 (87.8)	59 (84.3)	
Non - white	6 (20.7)	5 (12.2)	11 (15.7)	
Tobacco abuse, no. (%)				**0.51**
None	15 (51.7)	16 (39.0)	31 (44.3)	
Former	5 (17.2)	11 (26.8)	16 (22.9)	
Current	9 (31.0)	14 (34.1)	23 (32.9)	
Family History of UC, no. (%)				**0.72**
No	27 (93.1)	39 (95.1)	66 (94.3)	
Yes	2 (6.9)	2 (4.9)	4 (5.7)	
Charlson Comorbidity Index, no. (%)				**0.49**
≤ 4	19 (65.5)	21 (51.2)	40 (57.1)	
5 - 7	9 (31.0)	19 (43.9)	27 (38.6)	
≥ 8	1 (3.4)	2 (4.9)	3 (4.3)	
ASA Score, no. (%)				**0.26**
≤ 2	13 (44.8)	13 (31.7)	26 (37.1)	
≥ 3	16 (55.2)	28 (68.3)	44 (62.9)	
BPH medications, no. (%)				**<0.01**
No	24 (82.8)	9 (22.0)	33 (47.1)	
Yes	5 (17.2)	32 (78.0)	37 (52.9)	
Disease - specific characteristics				
Tumor size, no. (%)				**0.39**
Small (0.5 - 2.0 cm)	19 (65.5)	19 (46.3)	38 (54.3)	
Medium (2.0 - 5.0 cm)	8 (27.6)	16 (39.0)	26 (37.1)	
Large (> 5.0 cm)	2 (6.9)	4 (9.8)	6 (8.6)	
Tumor focality, no. (%)				**0.93**
Solitary	18 (62.1)	25 (61.0)	43 (61.4)	
Multiple	11 (37.9)	16 (39.0)	27 (38.6)	
Pathological Tumor Grade, no. (%)				**0.003**
Low - grade	19 (65.5)	12 (29.3)	31 (44.3)	
High - grade	10 (34.5)	29 (70.7)	39 (55.7)	
Pathological Tumor Stage, no. (%)				**0.41**
Ta	19 (65.5)	22 (53.7)	41 (58.6)	
T1	8 (27.6)	12 (29.3)	20 (28.6)	
Tis	2 (6.9)	7 (17.1)	9 (12.9)	
Post - resection Mitomycin C, no. (%)				**0.98**
No	22 (75.9)	31 (75.6)	53 (75.7)	
Yes	7 (24.1)	10 (24.4)	17 (24.3)	
Pathology - proven recurrence, no. (%)				**< 0.01**
No	27 (93.1)	19 (46.3)	46 (65.7)	
Yes	2 (6.9)	22 (53.7)	24 (34.3)	

Table 2 - Patient characteristics and outcomes stratified by the presence of a recurrence.

	No recurrence (n = 46)	Recurrence (n = 24)	Total (n = 70)	p - value
Sociodemographic and clinical characteristics				
Mean age, years (SD)	63.8 (11.4)	67.8 (11.8)	65.2 (11.6)	0.18
Mean BMI, kg / m2 (SD)	29.8 (7.1)	29.9 (6.2)	29.8 (6.8)	0.95
Race, no. (%)				**0.22**
White	37 (80.4)	22 (91.7)	59 (84.3)	
Non - white	9 (19.6)	2 (8.3)	11 (15.7)	
Tobacco abuse, no. (%)				**0.29**
None	18 (39.1)	13 (54.2)	31 (44.3)	
Former	10 (21.7)	6 (25.0)	16 (22.8)	
Current	18 (39.1)	5 (20.8)	23 (32.9)	
Family History of UC, no. (%)				**0.69**
No	43 (93.5)	23 (95.8)	66 (94.3)	
Yes	3 (6.5)	1 (4.2)	4 (5.7)	
Charlson Comorbidity Index, no. (%)				**0.93**
≤ 4	27 (58.7)	13 (54.2)	40 (57.1)	
5 - 7	17 (37.0)	10 (41.7)	27 (38.6)	
≥ 8	2 (4.3)	1 (4.2)	3 (4.3)	
ASA Score, no. (%)				**0.96**
≤ 2	17 (37.0)	9 (37.5)	26 (37.1)	
≥ 3	29 (63.0)	15 (62.5)	44 (62.9)	
BPH medications, no. (%)				**0.09**
No	25 (54.3)	8 (33.3)	33 (47.1)	
Yes	21 (45.7)	16 (66.7)	37 (52.9)	
Mean IPSS (SD)	8.2 (4.6)	13.3 (4.9)	9.9 (5.3)	< 0.01
Mean IPSS QoL (SD)	2.5 (1.4)	3.8 (1.0)	3.0 (1.4)	< 0.01
Mean IPSS Voiding (SD)	5.0 (2.8)	7.9 (2.6)	6.0 (3.1)	< 0.01
Mean IPSS Storage (SD)	3.2 (2.2)	5.4 (2.8)	3.9 (2.6)	< 0.01
Disease - specific characteristics				
Tumor size, no. (%)				**0.51**
Small (0.5 - 2.0 cm)	27 (58.7)	11 (45.8)	38 (54.3)	
Medium (2.0 - 5.0 cm)	16 (34.8)	10 (41.7)	26 (37.1)	
Large (> 5.0 cm)	3 (6.5)	3 (12.5)	6 (8.6)	
Tumor focality, no. (%)				**0.89**
Solitary	28 (60.9)	15 (62.5)	43 (61.4)	
Multiple	18 (39.1)	9 (37.5)	27 (38.6)	
Pathological Tumor Grade, no. (%)				**0.004**
Low - grade	26 (56.5)	5 (20.8)	31 (44.3)	
High - grade	20 (43.5)	19 (79.2)	39 (55.7)	
Pathological Tumor Stage, no. (%)				**0.001**
Ta	34 (73.9)	7 (29.2)	41 (58.6)	
T1	9 (19.6)	11 (45.8)	20 (28.6)	
Tis	3 (6.5)	6 (25.0)	9 (12.9)	
Post - resection Mitomycin C, no. (%)				**0.28**
No	33 (71.7)	20 (83.3)	53 (75.7)	
Yes	13 (28.3)	4 (16.7)	17 (24.3)	

total mean IPSS score did (OR: 1.26, 95% CI: 1.07 - 1.47, p = 0.005) (Table-5).

DISCUSSION

In this retrospective, cohort study of male patients with NMIBC, there was an association between the presence of moderate to severe LUTS on presentation (defined as an initial IPSS ≥ 8) with the risk of initial tumor recurrence on follow-up. Higher mean IPSS also correlated with an increased incidence of recurrence but subcategorization based on voiding versus storage symptoms did not show that one set was more strongly related to recurrence risk.

Table 3 - Predictors of pathology - proven tumor recurrence in the urinary tract based on the degree of LUTS.

	Multivariate			
	OR	95% CI		p - value
		Lower	Upper	
Mean age, years	1.01	0.95	1.08	0.75
Moderate or severe LUTS [IPSS ≥ 8] (reference: mild LUTS [IPSS < 8])	19.1	2.86	127	0.002
High - grade tumor (reference: low - grade)	1.06	0.22	5.02	0.95
Pathological Tumor Stage				
pT1 tumor (reference: pTa)	9.91	1.74	56.4	0.01
pTis tumor (reference: pTa)	10.4	1.32	82.3	0.026

Table 4 - Predictors of pathology - proven tumor recurrence in the urinary tract based on IPSS subcategories.

	Multivariate			
	OR	95% CI		p - value
		Lower	Upper	
Mean age, years	1.01	0.95	1.08	0.75
Mean IPSS Voiding	1.30	0.97	1.74	0.08
Mean IPSS Storage	1.20	0.84	1.71	0.31
High - grade tumor (reference: low - grade)	1.36	0.31	6.11	0.69
Pathological Tumor Stage				
pT1 tumor (reference: pTa)	7.35	1.41	38.4	0.018
pTis tumor (reference: pTa)	10.6	1.47	76.9	0.019

Table 5 - Predictors of pathology - proven tumor recurrence in the urinary tract based on overall IPSS.

	Multivariate			
	OR	95% CI		p value
		Lower	Upper	
Mean age, years	1.01	0.95	1.08	0.75
Mean IPSS	1.26	1.07	1.47	0.005
High - grade tumor (reference: low - grade)	1.39	0.31	6.14	0.67
Pathological Tumor Stage				
pT1 tumor (reference: pTa)	7.57	1.48	38.8	0.015
pTis tumor (reference: pTa)	10.4	1.44	75.1	0.020

We hypothesis this association may be related to increased urinary contact time of the bladder mucosa in patients with voiding dysfunction secondary to incomplete bladder emptying. The urogenous contact hypothesis was first introduced in the mid - 1970s and claims there is a connection between urinary contact time and the development of urothelial carcinoma of the bladder (10). In a study that looked at the association between fluid intake and the risk of bladder cancer in men, investigators analyzed 47.909 men and the amount of fluid they consumed (11). The authors determined that a higher fluid intake was associated with a reduced risk of bladder cancer. The authors hypothesized that this inverse relationship between fluid intake and bladder cancer was secondary to reduced urinary contact time with the bladder and less exposure to potentially harmful carcinogens. Silverman et al. additionally looked at the association between nighttime voiding and bladder cancer (10). This study similarly found an inverse relationship between nocturia and bladder cancer, stating that men and women who voided at least twice per night experienced a significant reduction in risk of malignancy. The authors hypothesized that those who void less at night have increased urinary contact time and thus a higher risk of bladder cancer.

In the typical age group that men develop bladder cancer (60 - 80 years), BPH can cause significant LUTS, such as urinary frequency, urgency, and hesitancy because of obstruction of the bladder. This can cause elevated post void residual (PVR) urine from incomplete bladder emptying, which may increase urinary contact time and exposure to carcinogens in the urine. Zhou et al. examined the risk of bladder cancer in relation to the severity of LUTS among 30.183 men from 1996 until 2010 using data from the Health Professionals Follow-up Study (12). Men with severe LUTS had a 64% higher risk of bladder cancer (relative risk [RR]: 1.64; 95% CI: 0.87 - 3.08) compared to men with no reported LUTS. Patients with both voiding and storage dysfunction had a significantly higher risk of bladder cancer (RR: 1.60; 95% CI: 1.00 - 2.56), and urinary hesitancy was the strongest individual urinary symptom associated with bladder cancer (RR: 2.21; 95% CI: 1.29 - 3.78).

Matsumoto et al. showed in an animal model that when rats have a surgically induced partial bladder outlet obstruction and a carcinogen is introduced into the water, there is a greater incidence of bladder cancer (13). No bladder cancer was found in the rats exposed to the carcinogen alone, but six out of the ten rats with partial bladder outlet obstruction and exposure to the carcinogen developed bladder cancer after eight weeks. Tseng et al. also reported that BPH was a significant independent risk factor for bladder cancer in men with type 2 diabetes in Taiwan using national reimbursement data from 1996 to 2009 (8). The incidences of bladder cancer were 258.77 and 69.34 per 100.000 person - years for patients with and without BPH, respectively.

Early resolution of BOO and lower PVR volume may decrease the recurrence rate of bladder tumors secondary to lower urinary contact time. Ham et al. observed that tumor recurrence was significantly lower, and time to recurrence was longer after simultaneous TURBT and transurethral resection of the prostate (TURP) in men with concurrent urothelial carcinoma of the bladder and BOO secondary to BPH causing LUTS (14). The 60 - month recurrence - free probability was 52% compared to 43% ($p < 0.01$) in patients who had TURBT alone without any resolution of their BPH / BOO. There was no difference in progression rates between the two groups. A similar study from Europe corroborated this finding, showing a reduced 5 - year recurrence rate (56% vs. 80%, $p < 0.01$) in men diagnosed with Tis, Ta, or T1 urothelial carcinoma of the bladder and BPH / BOO who underwent TURBT and TURP in the same setting versus TURBT alone (15). Early resolution of bladder outlet obstruction not only decreased tumor recurrence rate, but also had a positive effect on patient quality of life. Two meta - analysis have additionally reinforced suggestions that simultaneous TURBT and TURP may be beneficial in reducing tumor recurrence in patients with both superficial urothelial carcinoma of the bladder and BOO secondary to BPH. Luo et al. evaluated pooled data from 483 patients in six eligible clinical trials and found that the recurrence rate in the simultaneous resection group was

statistically significantly lower than in the control group (TURBT alone) (OR = 0.67; 95% CI = 0.52 to 0.88, p = 0.003) (16). Li et al. also reported on pooled data from eight studies, including seven non - randomized concurrent controlled trials and one randomized controlled trial, involving a total of 1.372 patients (17). Meta - analyses showed that in the TURBT + TURP group, overall recurrence rates were lower (OR = 0.76; 95% CI = 0.60 - 0.96; p = 0.02), and this difference was statistically significant. The postoperative recurrence rate in the prostatic fossa / bladder neck (OR = 0.96; 95% CI = 0.64 - 1.45; p = 0.86) and bladder tumor progression rates (OR = 0.96; 95% CI = 0.49 - 1.87; p = 0.91) were similar between the TURBT + TURP and TURBT groups, and the difference was not significant. Both sets of authors, therefore, concluded that for patients with NMIBC and BPH / BOO, simultaneous resection may reduce the recurrence rate. Combined TURBT and TURP may be a reasonable option in NMIBC patients who present with significant urinary symptoms.

Our study does have several limitations. It is underpowered with only 70 male patients with NMIBC in our study population with limited mean follow-up of only 31.7 months. We were, however, very selective in our inclusion criteria to minimize confounding, excluding patients with histological variants, prior history of urothelial carcinoma, and non - bladder primary tumors.

Additionally, we did not have PVR volumes available via bladder scan or post - void catheterization for our study population. We were, therefore, unable to objectively measure the degree of incomplete bladder emptying across our study population for male patients with varying levels of LUTS, and we could not correlate these volumes with the recurrence rate of urothelial carcinoma. Only subjective measures of voiding dysfunction based on patient self - reported IPSS were abstracted.

Finally, given the study's retrospective design, there is the possibility of bias via inverse causality. In other words, men who present with NMIBC and bothersome urinary symptoms had a higher grade and stage of tumor that would be more prone to recurrence due to worse underlying disease rather than ongoing urinary symptoms causing the recurrence.

CONCLUSIONS

In this study, we reported that the presence of moderate or severely symptomatic LUTS in men at the time of diagnosis is associated with increased recurrence rates of NMIBC based on surveillance cystoscopy, imaging, and histological confirmation. Further evaluation of this hypothesis with objective measurements of voiding dysfunction such as PVR volumes should be considered. Additional prospective studies with larger sample sizes and longer term follow-up are necessary to corroborate these findings.

ABBREVIATIONS

ASA = American Society of Anesthesiologists
BCG = Bacillus Calmette - Guérin
BOO = bladder outlet obstruction
BPH = benign prostatic hyperplasia
CCI = Charlson Comorbidity Index
CI = confidence interval
CIS = carcinoma in situ
IPSS = International Prostate Symptom Score
LUTS = lower urinary tract symptoms
NMIBC = non - muscle invasive bladder cancer
OR = odds ratio
PVR = post void residual
QoL = quality of life
RR = relative risk
SPSS = Statistical Package for the Social Sciences
TURBT = transurethral resection of bladder tumor
TURP = transurethral resection of the prostate
UC = urothelial carcinoma

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CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Can Neutrophil-to-Lymphocyte ratio predict the response to BCG in high-risk non muscle invasive bladder cancer?

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ABSTRACT

Objectives: To evaluate the neutrophil-to-lymphocyte ratio (NLR) as a prognostic factor for response of high risk non muscle invasive bladder cancer (HRNMIBC) treated with BCG therapy.
Materials and Methods: Between March 2010 and February 2014 in a tertiary center 100 consecutive patients with newly diagnosed HRNMIBC were retrospectively analyzed. Patients were divided according to NLR value: 46 patients with NLR value less than 3 (NLR < 3 group), and 54 patients with NLR value more than 3 (NLR ≥ 3 group). At the end of follow-up 52 patients were high grade disease free (BCG-responder group) and 48 patients underwent radical cystectomy for high grade recurrence or progression to muscle invasive disease (BCG non-responder group). The average follow-up was 60 months. Intervention: analysis and correlation of preoperative NLR value with response to BCG in terms of recurrence and progression.
Results: The optimal cut-off for NLR was ≥ 3 according to the receiver operating characteristics analysis (AUC 0.760, 95% CI, 0.669-0.850). Mean NLR value was 3.65 ± 1.16 in BCG non-responder group and 2.61 ± 0.77 in BCG responder group (p = 0.01). NLR correlated with recurrence (r = 0.55, p = 0.01) and progression risk scores (r = 0.49, p = 0.01). In multivariate analysis, NLR (p = 0.02) and EORTC recurrence risk groups (p = 0.01) were associated to the primary endpoint. The log-rank test showed statistically significant difference between NLR < 3 and NLR ≥ 3 curves (p < 0.05).
Conclusions: NLR value preoperatively evaluated could be a useful tool to predict BCG response of HRNMIBC. These results could lead to the development of prospective studies to assess the real prognostic value of NLR in HRNMIBC.

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Urinary Bladder Neoplasms; Neutrophils; Lymphocytes

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INTRODUCTION

Worldwide, bladder cancer is the ninth most commonly diagnosed malignancy and the 13th cause of cancer deaths in 2015 (1).

Bladder cancer is the second most frequent genitourinary tumor. At first diagnosis of 75 - 85% patients have a mucosal (stage Ta, Carcinoma in situ) or submucosal neoplasia (stage T1) (2).

The challenge in treating non - muscle - invasive bladder cancer (NMIBC) is to preserve the bladder and its function, accepting the risk of recurrence (up to 78% of cases) and the risk of progression to muscle - invasive disease (up to 45% of cases).

The identification of patients with higher risk of recurrence and progression is mandatory

in order to predict oncological outcomes and for optimal tailored therapeutic decision - making.

The gold standard treatment for NMIBC is represented by transurethral resection of bladder tumor (TURBT) and a re - TURBT when indicated (any high grade disease except Cis, any T1, incomplete TURBT or absence of muscle in the specimen), followed by adjuvant intravesical chemo - or immunotherapy.

European Organization of Research and Treatment of Cancer (EORTC) risk tables (3) suggested a stratification of patients in low, medium and high risk of recurrence and progression, and a relative treatment strategy.

The treatment of high-risk patients is based on the induction course of intravesical immunotherapy with BCG (Bacillus Calmette-Guerin) followed by maintenance course for at least one year (4).

Many predictor tools have been analyzed in the context of cancer development and progression. A high neutrophil - to - lymphocyte ratio (NLR) was already consistently associated with locally advanced disease and worse general and cancer-specific survival rates in several solid tumors (5).

A high NLR seems to represent an independent prognostic factor of recurrence and progression of disease in patients with NMIBC (6). NLR may be helpful to better identify patients who would be optimally treated and cured with BCG and patients in whom conservative treatment would probably be ineffective.

The purpose of this study is to evaluate whether preoperative NLR measurement may add useful information for the best disease management and for prediction of response to BCG in high risk non muscle invasive bladder cancer (HR - NMIBC).

MATERIALS AND METHODS

We retrospectively analyzed 100 consecutive patients treated in our Clinic for a first diagnosis of high - risk NMIBC (according to EORTC and EAU guidelines) between March 2010 and February 2012. We excluded patients with previous history of low risk NMIBC.

All these patients underwent an intravesical BCG schedule consisting of one induction course (6 weekly instillations) followed by one year of monthly maintenance course.

In all patients, the histological specimen documented a pure urothelial cancer with detrusor muscle included in the resection; we did not analyzed patients with other histological variants.

All high grade pTa and pT1 patients underwent reTURBT according EAU guidelines.

For all patients the follow-up was 60 months.

At the end of follow-up 52 patients were high grade disease free (BCG - responder group) and 48 patients underwent radical cystectomy for high grade recurrence or progression to muscle invasive disease) (BCG non - responder group).

Patients were divided according to their NLR value (Table-1): 46 patients with NLR value less than 3 (NLR < 3 group), and 54 patients with NLR value more than 3 (NLR ≥ 3 group).

Three patients developed a solitary or concurrent upper tract urothelial carcinoma (UTUC) disease: two patients (4.3%) in NLR < 3 group and 1 patient (1.8%) in NLR ≥ 3 group; two patients (3.8%) in BCG - responder group and 1 patient (2.1%) in BCG - non responder group.

In all patients, the BCG strain used was Seed RIVM by Medac® (derived from seed 1173 - P2, 2 x 10 to 3 x 10 viable units). The Medac® - BCG powder was re - suspended with 50 mL of 0.9% normal saline and introduced into the bladder via a 10-12 French urethral catheter. Patients were instructed to hold the drug in the bladder for two hours.

Four experienced urologists performed all the diagnostic cystoscopies and all the TURBTs.

All specimens were analyzed by an experienced dedicated uropathologist.

The 2009 TNM classification (7) and the 2004 WHO grading system (8) were used for histologic reports.

Recurrence was defined as the first histologically confirmed high grade NMBIC recurrence; progression was defined as the development of muscle - invasive bladder cancer (MIBC).

Diagnostic cystoscopies, TURBTs and eventual reTURBTs were performed using NBI (Narrow Band Imaging) technology.

All the analyzed patients completed the induction six - weekly BCG instillation schedule (in order to avoid bias related to the intravesical immunotherapy toxicity).

At the end of the induction course all patients underwent endoscopic evaluation, voiding and washing urinary cytology, transurethral resection (TUR) of any suspected area. Random biopsies including prostatic urethra for patients were performed if indicated.

In case of high grade tumor recurrence or progression to muscle invasive disease during follow-up, patients were considered as BCG failure according to EAU guidelines and underwent radical cystectomy. We excluded all cases of BCG--intolerance (9). Patients with low grade low stage BCG - relapsing diseases were considered in the BCG responder group considering that they should not be considered as "BCG failure" according to EAU guidelines (3).

Patients with complete response after induction course underwent BCG maintenance course for at least 1 year and subsequent endoscopic follow-up every 3 months for the first two years and then every 6 months according the EAU guidelines (3).

All the analyzed patients completed the induction six - weekly BCG instillation; no event of therapy discontinuation was reported. We reported 5 cases of therapy discontinuation during the last instillations of the maintenance cycle (due to severe BCG - related complications): 3 patients (6.5%) in NLR < 3 group and 2 patients (3.7%) in NLR ≥ 3 group; 3 patients (5.8%) in BCG - responder group and 2 patient (4.2%) in BCG - non responder group; these patients therefore underwent cystoscopic, cytologic and radiologic evaluations: all of them were high grade disease - free, so they continued regular follow-up.

For each patient, we reported the preoperative hematologic and chemical data, including the total number of white blood cells (WBC), neutrophils (N) and lymphocytes (L). Patients underwent blood sampling the day before the TURBT, in the morning, after at least 6 hours of fasting. We enrolled only patients without hematuria in order to avoid any sort of bias, especially in terms of total blood count. The NLR ratio was calculated by dividing the value of N by the value of L.

The preoperative NLR measurement collected at the first TURBT was the reference value for each patient.

We used a receiver operating characteristic (ROC) curve to determine an appropriate cut - off value.

All patients were classified into two groups according to the NLR. The X2 test was used to verify the significance of the correlation between the NLR and the clinic - pathological characteristics.

Patients with preoperative diagnosis of active infection, hematologic neoplasms or unexplained leukocytosis, presence of other neoplasms, prior systemic chemotherapy were excluded from the study.

The groups were compared according to the following data: age, sex, stage and grade of tumor, size and number of tumors, presence of carcinoma in situ, NLR.

In addition, patients were classified according to the EORTC risk tables (3) for the recurrence risk score (1-4, 5-9, ≥ 10) and for the progression risk score (2-6, 7-13, and ≥ 13). No patient had a recurrence or progression risk score of zero and all patients scored zero regarding "prior recurrence rate" because all of them had newly diagnosed bladder cancer.

The aim of the study was to identify a potential role of NLR as an independent prognostic factor for the response to endovesical BCG therapy.

Categorical variables were summarized using actual counts and percentages; the continuous variables using the mean ± standard deviation.

Parametric and nonparametric variables were evaluated using the t - test and the chi square test, respectively.

Logistic regression was used to determine independent predictors of BCG response.

The X2 distribution was used for categorical data. Pearson's test was used for the correlation analysis. Statistical significance was considered at $p < 0.05$.

Kaplan Meier curves and log rank test were built in order to evaluate cancer free survival between the two groups.

All patients provided informed written informed consent with guarantees of confidentiality.

The protocol for the research project was approved by the local Ethics Committee and it conformed to the provisions of the Declaration of Helsinki (as revised in Fortaleza, Brazil, October 2013).

RESULTS

The baseline patient's characteristics are summarized in Table-1. The median age of patients was 67.5 ± 10.7 years.

The mean value of NLR in all patients was 3.17 ± 1.12.

The mean NLR value was 2.61 ± 0.77 in BCG - responder group and of 3.65 ± 1.16 in BCG - non

Table 1 - Baseline characteristics based on NLR value.

Variables	General	NLR < 3	NLR ≥ 3	p value
N° of patients	100	46	54	
Median age**, years ± SD	67.5 ± 10.7	68.6 ± 10.8	66.7 ± 10.5	> 0.05
Sex*, n° of pts (%)				**> 0.05**
Male	87 (87%)	39 (84.8%)	48 (89.6%)	
Female	13 (13%)	7 (15.2%)	6(10.4%)	
NLR**, value ± SD	3.17 ± 1.12	2.32 ± 0.41	3.90 ± 0.88	0.01
Pathological stage*, n° of pts (%)**				**> 0.05**
Ta	11 (12%)	3 (6.5%)	8 (14.8%)	
T1	73 (73%)	35 (76.1%)	38 (70.4%)	
solitary Cis	16 (15%)	8 (17.4%)	8 (14.8%)	
Concomitant Cis*, n° of pts (%)	25 (25%)	2 (4.3%)	23 (42.6%)	0.01
No. of tumors*, n° of pts (%)				**0.01**
1	48 (48%)	35 (76.1%)	13 (24.1%)	
≥ 2	52 (52%)	11 (23.9%)	41 (75.9%)	
Tumor size (mm)*, n° of pts (%)				**0.01**
< 30	78 (78%)	42 (91.3%)	36 (66.7%)	
≥ 30	22 (22%)	4 (8.7%)	18 (33.3%)	
Recurrence risk score**, value ± SD	5.5 ± 2.3	4.2 ± 1.7	6.5 ± 2.2	0.01
Progression risk score**, value ± SD	12.1 ± 3.9	9.7 ± 2.2	14.2 ± 3.9	0.01
EORTC recurrence risk*, class (%)**				**0.01**
1-4	39 (39%)	29 (63.1%)	10 (18.5%)	
5-9	55 (55%)	17 (36.9%)	38 (70.4%)	
≥ 10	6 (6%)	0 (0%)	6 (11.1%)	
EORTC progression risk*, class (%)**				**0.01**
2-6	5 (5%)	3 (6.5%)	2 (3.7%)	
7-13	58 (58%)	40 (87%)	18 (33.3%)	
≥ 14	37 (37%)	3 (6.5%)	34 (63%)	

SD = standard deviation; Pts: patients; **NLR =** Neutrophil / Lymphocyte Ratio; **Cis =** Carcinoma In Situ; **EORTC =** European Organization for Research and Treatment of Cancer; **Test =** chi-square*; t-student**, ANOVA***

responder group (p value: 0.01), and 2.32 ± 0.41 in NLR<3 group and 3.90 ± 0.88 in NLR ≥3 (p value: 0.01).

After 60 months of follow-up, all patients in BCG-responder group were cancer-free, while all patients in BCG-non responder group underwent radical cystectomy for recurrence of high-grade NMIBC (n = 31) or for progression to muscle-invasive disease (n = 17); in 12 cases (70%) with evidence in the post-operative histopathological specimen of pT2, in 4 cases (25%) with pT3 and in 1 patient (5%) with pT4 disease for involving of prostatic stroma at the level of prostatic urethra.

According to the ROC analysis, the optimal cut-off of NLR was ≥ 3 (area under the curve [AUC] 0.760, 95% CI, 0.669-0.850, sensitivity 80.0%, specificity 72.0%, PPV 74.0%, NPV 78.0%, OR 10.29, RR 3.36, +LR 2.85, p value 0.01).

We reported a linear correlation between NLR value and recurrence risk score (r=0.55, p=0.01) and progression risk score (r = 0.49, p = 0.01) considered as continuous variables (Figure-1).

Moreover, we reported a statistically significant difference in the value of NLR among patients with different recurrence (p = 0.01) and progression risk scores (p = 0.01) considered as categorical variables.

Recurrence/progression rates increased with the increase of NLR values: 15.4% in patients with NLR between 1 and 2, 30.3% in patients with NLR between 2 and 3, 62.5% in patients with NLR between 3 and 4, and 78.6% in patients with NLR higher than 4 (p < 0.05).

We built Kaplan-Meier cancer free survival curves for patients with NLR < 3 and NLR ≥ 3: the log-rank test showed a statistically significant difference between the two curves (p < 0.05) (Figure-2).

In the multivariate analysis, prognostic factors were analyzed in order to weigh their role in relation to the primary endpoint; in this analysis we considered NLR and EORTC risk categories according relative scores (1-4, 5-9 and ≥ 10 risk groups for recurrence; 2-6, 7-13, ≥ 14 risk groups for progression): NLR (p = 0.02) and EORTC recurrence risk groups (p = 0.01) were associated, while EORTC progression (p = 0.11) risk groups were not associated (Table-2).

At the end of follow-up we reported higher recurrence/progression rates in case of higher NLR values. NLR values increased with the increase in scores: in 1-4, 5-9 and ≥ 10 recurrence risk groups NLR values were 2.60 ± 0.84, 3.44 ± 1.11, and 3.71 ± 0.38, respectively (p value: 0.01); in 2-6, 7-13 and ≥ 14 progression risk groups NLR values were 2.66 ± 0.41, 2.89 ± 1.02 and 3.79 ± 1.26, respectively (p value: 0.01).

At the end of follow-up in BCG- responder group there was no cancer-related death while in BCG-non responder group the cancer specific survival rate was 96.2%; the 2 patients that died presented an average NLR value of 4.8, statistically different compared to disease-free patients (p = 0.01) and patient treated with radical cystectomy (p = 0.01).

Figure 1 - Correlation between NLR and recurrence risk score and progression risk score.

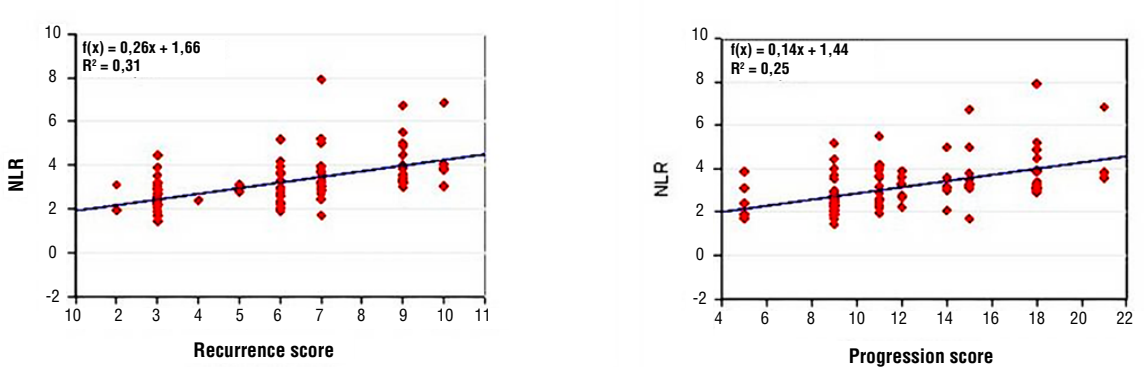

Figure 2 - Kaplan-Meier cancer free survival curves for patients with NLR< 3 and NLR ≥ 3.

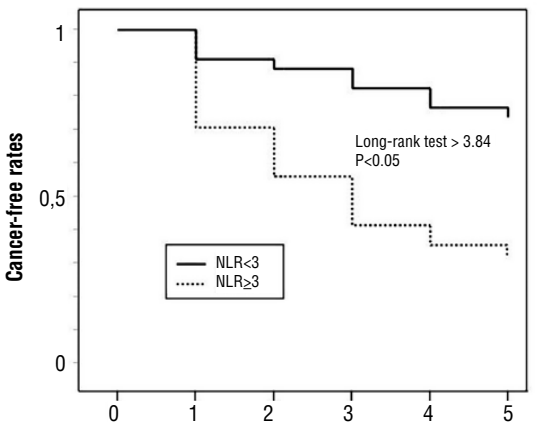

Table 2 - Logistic regression analysis for response to BCG.

Factors	B	S.E.	t	p	B %95 C.I.	
					Lower	Upper
NLR*	0.077	0.035	2.226	*0.02*	0,008	0,147
EORTC recurrence risk**	0.152	0.048	3.143	*0.01*	0,056	0.248
EORTC progression risk**	0.202	0.122	1.65	*0.10*	-0.041	0.444

* continuous variable; ** categorical variable

DISCUSSION

The prognostic role of NLR has already been extensively analyzed in many solid tumors but the underlying mechanism explaining the association of a high NLR and poor prognosis / poor outcomes of cancer patients is poorly known (10).

A potential mechanism has been identified in the association between high NLR and inflammation. The systemic inflammatory response stimulated by the neoplasia involves a pro-tumor inflammatory state, leading an active role of systemic inflammation in tumor growth, recurrence, and progression. Many inflammatory indexes (PCR, Platelet/Lymphocyte ratio - PLR -, albumin levels, fibrinogen levels, etc.) obtained from blood tests were associated with outcomes of many cancers.

Neutrophils and lymphocytes have an inhibitory and activating action, respectively, on the immune system: that is why they might reflect the inflammatory and immune response of the host.

Inflammatory response induces neutrophilia, lymphocytopenia and high excretion of pro-angiogenetic factors, growth factors, anti-apoptotic factors, all stimulating tumor growth and progression (11). Neutrophilia as an inflammatory response inhibits the immune system by suppressing the cytolytic activity of immune cells such as lymphocytes, activated T cells and natural killers cells (12, 13).

The increase in tumor lymphocyte infiltration has been associated with better responses to cytotoxic treatments and better prognosis of cancer patients. Inflammatory cytokines and chemokines can be produced by both tumor and host cells (such as lymphocytes) contributing to tumor progression.

NLR might therefore represent a systemic inflammation parameter and efficient biomarker of the host-tumor interaction (11). A high NLR value could reflect both an increased neutrophil-dependent inflammatory reaction and a diminished lymphocyte-dependent immune response (14).

An increase in NLR was associated with an increase of peritumoral infiltration of macrophages and increased interleukins and cytokines production (IL-1ra, IL6, IL7, IL8, IL9, IL12, IFN-gamma, etc.). Neutrophils and other cells secrete tumor growth promoting factors (VEGF, HGF, IL6, IL8, MMPs, elastanes) thus contributing to microenvironment of tumor stimulation (for example, IL6 has been shown to be at higher concentrations in 13 different types of neoplasia and associated with higher tumor stage and adverse prognosis).

In vitro and in vivo studies showed that the systemic and local responses (at the bladder wall) to BCG are represented by an increase in T lymphocytes, with a predominance of T helper / inducer cells.

Although studies demonstrated BCG efficacy (and safety) of immunocompromised patients, studies on the immunological mechanism of BCG therapy showed that an intact immune system (particularly of the cellular system) is required for anti-tumor activity; clinical and laboratory evidence showed that BCG interaction with immune system produces a relative systemic immunity to BCG, necessary for its effectiveness (15).

Previous studies assessed the NLR value in patients with MIBC undergoing radical cystectomy (16): correlations were found between high levels of NLR and diagnosis of MIBC at TURBT and with non-organ confined tumor (17).

In the study of Mano et al. higher NLR values were associated with unfavorable tumor characteristics (high grade of differentiation, T1 tumor) in 122 patients with new NMIBC diagnosis.

In our study, patients with NLR ≥ 3 presented statistically significant worse tumor characteristics (negative prognostic factors) such as concomitant Cis ($p<0.01$, OR 16.3), multifocality ($p<0.01$, OR 10), tumor size >3 cm ($p<0.01$, OR 5.2) compared to patients with NLR <3.

Higher NLR values were associated with tumor progression and recurrence in univariate and multivariate analyses adjusted for EORTC risk groups (16). We observed linear correlations between NLR value and patient's EORTC classes (Figure-1).

In a cohort of 86 patients, Albayrak et al. reported a significant difference in NLR values between recurrence and progression risk score groups, with mean NLR values progressively higher as the risk class increased. In this study, however, patients' age was statistically different between recurrence and progression risk score groups and, after correcting for the statistical effect of age on scores, the relationship between NLR and recurrence and progression risk scores was no longer significant. Authors suggested to correct the NLR value according to patients' age in order to avoid deceitful results (18). We evaluated NLR according to EORTC risk score and we reported their linear correlation. Unlike other studies (16, 19), patients' age was not correlated with NLR values and EORTC risk scores, so our results did not need correction for the patients' age.

In the study of Cimen et al. in a cohort of 271 patients the NLR value was associated with the T1 pathological stage: patients with NLR >1.8 had 1.5 times higher risk to develop a lamina propria infiltrating tumor. [18] In our study, all patients with NLR<1.8 had a lamina propria infiltrating cancer, so we could not confirm or compare these data, maybe due to the specific subgroup of HRNMIBC patients we considered (Cimen et al. included papillary urothelial neoplasm of low malignant potential – PUNLMP - and low grade low stage bladder cancer patients).

In a cohort of 178 patients, Favilla et al. prospectively assessed the role of NLR as biomarker of NMIBC in terms of prognostic marker of disease recurrence, reporting a statistically significant association of higher NLR value (with a cut-off ≥ 3) with recurrence (such as in our study) but not with progression (differently from our results) (20).

In our study patients with higher NLR showed higher recurrence/progression rates than those with lower NLR: 15.4% of recurrence/progression rate for patients with NLR values between 1 and 2, 32.4% for NLR values between 2 and 3, 83.3% for NLR values between 3 and 4, 85.7% for NLR value more than 4.

Qzyalvachi et al. reported a statistically significant correlation between recurrence of pT1 HGNMIBC and NLR with cut-off of NLR ≥ 2.43 in 166 patients. In the multivariate logistic regression analysis NLR, tumor number and smoking were determined as independent predictors of re-

currence while no statistically significant correlation was reported between NLR and progression (18). In our study the multivariate analysis showed that NLR value (p=0.02) and EORTC recurrence (p=0.01) risk groups were independent factors of non-response to BCG (intended as high-grade recurrence or progression disease); even in our study progression risk groups were not independent factors of non-response to BCG (p=0.10)

D'Andrea et al. evaluated the prognostic role of NLR in patients with primitive NMIBC. The optimum cut-off value of NLR was 3. In univariate and multivariate analysis, NLR≥3 was significantly associated with recurrence free survival (RFS) and progression free survival (PFS) and with outcomes in patients treated with BCG. In this retrospective study on 918 patients, authors suggested the integration of NLR into a predictive model to predict RFS and PFS in patients with NMIBC (19).

Mbeutcha et al. showed a relationship between oncological outcomes of NMIBC and markers of systemic inflammatory response, including NLR. Authors evaluated retrospectively 1.117 patients and reported a statistically significant association between high NLR values and disease recurrence and progression; this association was confirmed in the analysis of a subgroup of 300 patients treated with BCG. Even these authors suggested the introduction of NLR in prognostic models (21).

The EAU guidelines for UTUC management already considers NLR as a prognostic tool in the preoperative assessment (22), nevertheless our results and literature suggest a pivotal role for this value in bladder cancer management.

In a retrospective study on 1.551 patients, Kang et al. reported a significant association of high preoperative NLR with host-related outcomes (overall and cancer specific survival) but not with PFS and RFS (23). In this larger series of patients a linear correlation of NLR with RFS and PFS was not reported, but authors reported a significant association between this factor and overall survival and cancer specific survival, still validating the prognostic power of NLR in bladder cancer.

In our cohort of patients the mean higher values of NLR seemed to be compliant with the specific population of patients in exam (high grade, pT1, presence of Cis, etc.). NLR was statistically higher in patients who underwent radical cystectomy; in fact patients with NLR ≥3 showed a 2.85 times higher risk to be treated with radical cystectomy.

Our aim was to add a prognostic factor for the definition of the particular subgroup of patients with "highest risk" NMIBC (3) who, according to EAU guidelines (LE: 3, Strength rating: Strong), could benefit from radical surgery even after the first diagnosis given the high risk of recurrence and progression.

In addition to the other already known prognostic factors, NLR could help to inform patient, in a shared decision making process, about the aggressiveness of the neoplasm, providing realistic probabilities of success/failure of the conservative treatment.

It is widely known that this group of patients require the best therapeutic option (BCG) and a close follow-up since conservative intravesical treatment has a high probability of failure (up to 62% of recurrence, up to 45% of progression, in our specific cohort of patients, according EORTC class risk).

According to our experience the NLR report could allow to better identify patients for whom radical cystectomy might be the only form of curative treatment. This could also allow to precociously begin a psychological support for the patient in prevision of a major surgery and all related changes on the quality of life (QoL) (24).

Other advantages of using the NLR value are: easy applicability, wide availability and low cost. In the literature, various NLR cutoff values were evaluated and applied (25). This implies the need to interpret the results carefully as the cut-off value was chosen in each specific cohort by testing different discrimination values with relative different sensitivities and specificities. In the light of these considerations, an ideal and generalizable NLR value is still far from being well defined.

Some limitations of our study were: small number of patients; individual preoperative systemic inflammatory response tests; retrospective study performed in a single tertiary center with relative unavoidable selection biases; the lack of in vivo and / or in vitro studies in order to validate our hypotheses.

CONCLUSIONS

Our data showed that a high value of NLR evaluated preoperatively might be helpful to predict the BCG response and therefore provide critical information for the clinical management of high-risk NMIBC patients together with the prognostic factors already known.

In order to give greater significance to our results, prospective studies are needed for validating the NLR as a real prognostic factor of the high-risk NMIBC and for identifying the ideal and reproducible NLR cut-off value.

COMPLIANCE WITH ETHICAL STANDARDS

This research study involving human subjects was registered in the publicly accessible EudraCT (European Union Drug Regulating Authorities Clinical Trials) database before recruitment of the first subject with the number 2018-001276-38.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Initial experience of video endoscopic inguinal Lymphadenectomy in a center located at northeast brazilian region

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ABSTRACT

Introduction: Video endoscopic inguinal lymphadenectomy – VEIL – has emerged as an alternative to reduce post-surgical complications (PSC) in patients with penile cancer submitted to inguinal lymphadenectomy (IL). In some series, these PSC are observed in more than 50% of patients. The objectives of the present study are to describe the initial experience of VEIL in a Hospital in Teresina, PI, Brazil, and to analyze PSC incidence.

Material and Methods: Retrospective descriptive study of patients submitted to VEIL from March 2014 to November 2015. Data were collected regarding surgical time, bleeding, complications, lymph node number, conversion, global complications, drainage time, cellulitis, lymphocele, cutaneous necrosis, miocutaneous necrosis and hospitalization time.

Results: 20 lower limbs of 11 patients were operated. Mean age was 51.4 (24-72) years. Mean surgical time was 85 (60-120) minutes. No patient showed intrasurgical complications, bleeding > 50 mL or conversion. Three surgeries evolved with lower limb edema, 2 with lymphoceles and one patient had cutaneous necrosis and another bulging of surgical wound. Mean time of hospitalization was 4 (2-11) days. A mean of 5.8 (1-12) lymph nodes were dissected in each surgery.

Conclusion: VEIL is a safe and easy technique with lower incidence of PSC that can be reproduced in small centers.

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Penile Neoplasms; Lymph Node Excision; Minimally Invasive Surgical Procedures

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INTRODUCTION

The main site of metastasis of penile cancer is inguinal lymph nodes. Around 30% of patients show inguinal involvement at diagnosis, and this is a determinant factor of mortality related to this type of tumor (1, 2). Open inguinal lymphadenectomy (IL) is considered the gold standard of care for lymph node metastasis of penile cancer (3). However, this procedure has a high morbidity, including skin necrosis or post-operatory infection of surgical wound. Also, depending on the extension of lymphadenectomy, a higher frequency of lower limb edema, lymphocele, lymphedema and lymphorrea is observed (4).

In 2006, Tobias-Machado et al. described the Video Endoscopic Inguinal Lymphadenectomy

– VEIL, in order to reduce morbidity, but maintaining the same oncologic principles of conventional technique (5). Since then, several series were published with good results. VEIL is easy and safe to perform in certain patients, but, although with promising initial results, this surgery is still not enough widespread and currently is being more performed in referral centers.

The objectives of the present study are to describe the initial experience with VEIL in a tertiary center in the northeast region of Brazil, to analyze the incidence of post-surgical complications, to critically analyze the technique and to verify its reproducibility in a median size hospital.

MATERIALS AND METHODS

This is a retrospective and descriptive study, approved by the Ethical and Research Committee of the Institution under the number 61046316.6.0000.5584. Data were exclusively obtained in the charts. The study was funded only by the authors.

The study was performed at the Hospital São Marcos, in Teresina, PI, Brazil. Patients were operated from March 2014 to November 2015. Lymphadenectomy was performed in men with epidermoid carcinoma submitted to previous penis amputation and with high risk of lymph node metastasis. Surgery was performed by three experienced urologists and after at least an interval of four weeks following amputation. Indication criteria included: T2 and/or G2 tumors and/or with vascular or perineural invasion. No patient showed peripheral lymphadenopathy.

Patients were operated according to Tobias-Machado technique: 1) positioning of lower limb abducted and extended; 2) introduction of 3 ports in the femoral triangle; 3) obtaining a work space with gas; 4) separation of skin using electric scalp; 5) identification and dissection of saphenous vein magna up to oval fossa; 6) identification of femoral artery; 7) distal ligature of lymph node block on the vertex of the femoral triangle; 8) release of lymph node tissue until the great vessels above femoral surface; 9) distal ligature of saphenous vein magna; 10) control of saphenous-femoral junction; 11) final release of surgical specimen and field hemostasis; 12) removal through initial orifice; 13) vacuum drainage and closure of incisions.

Demographic data were evaluated and summarized in tables. Clinical data were evaluated and summarized in tables. The following peri-operatory data were analyzed: surgical time, bleeding, complications, lymph node count, and conversion to open surgery. Also, post-surgical data were also analyzed: global complications, drainage time, cellulitis, lymphoceles, cutaneous necrosis, miocutaneous necrosis and time of hospitalization. Intra-operatory bleeding was estimated according to the aspirated volume during the procedure.

Data were analyzed at R-Project. In order to compare means and proportions of the selected literature results with those of the present study, it was used Analysis of Variance (ANOVA) with Tukey post-test. Normality assumption was verified by the Shapiro-Wilk test, and all variables were approximately normal. Significance level was 5% (p-value<0.05) (6).

RESULTS

Main demographic and clinical and pathological characteristics of patients are summarized in Table-1. Mean age was 51.4 (24-72) years. Eleven patients were operated: 6 were submitted to bilateral VEIL (non-simultaneous), 3 to simultaneous bilateral VEIL, and 2 unilateral VEIL with open IL in the contralateral limb, totalizing 20 surgeries. Three patients (27.2%) showed compromised lymph nodes and in 8 (72.8%) no metastasis was identified. Positive lymph node rate was 8.3%. Mean follow-up time was 111 (2-180) weeks. One patient died due to pulmonary metastatic disease 22 weeks after surgery and another 83 weeks after surgery, due to local recurrence. Two patients were lost to follow-up, and the remaining are alive, without signs of active disease, with periodic consultations.

Main surgical results are summarized in Table-2. Mean operatory time was 85 (60-120) minutes. A mean of 5.8 (1-12) lymph nodes were dissected in each surgery. Intra-operatory bleeding of all procedures was lower than 50 mL, therefore

Table 1 - Demographic, clinical and pathological characteristics of patients.

Number	1	2	3	4	5	6	7	8	9	10	11
Age at diagnosis	46	64	44	60	55	55	72	24	38	46	62
Histologic type	epidermoid	epidermoid	epidermoid	epidermoid	epidermoid	epidermoid	epidermoid	epidermoid	epidermoid	epidermoid	epidermoid
Pathologic staging	T2	T2	T2	T3	T2	T3	T1	T2	T2	T2	T3
	N0	N0	N0	N0	N0	N0	N0	N1	N1	N0	N1
	M0	M0	M0	M0	M0	M0	M0	M0	M0	M0	M0
	G1	G2	G1	G3	G3	G1	G3	G2	G1	G1	G3
Technique	SBV	NSBV	OU + UV	NSBV	NSBV	NSBV	NSBV	NSBV	SBV	SBV	OU + UV
Number of positive lymph nodes	0	0	0	0	0	0	0	2	1	0	6
Follow up (weeks)	83	136	135	23	111	180	2	117	59	62	148
Current status	D	A	A	D	A	A	L	A	L	A	A

SBV = simultaneous bilateral **VEIL; NSBV =** non-simultaneous bilateral **VEIL; OU =** open unilateral; **UV =** unilateral VEIL; **D =** death; **A =** alive; **L =** loss of follow-up

considered negligible. No patient presented intra-operatory complication or conversion to open surgery.

Main post-surgical complications are described in Figure-1. Mean hospitalization time was 4 (2-11) days. One patient showed cutaneous necrosis of surgical wound and needed antibiotics. Mean drainage time was 8 days; some patients were discharged with drain in position due to copious secretion. The drain was removed during post-surgical ambulatory follow-up.

DISCUSSION

Squamous cell penile carcinoma is a rare disease, especially in developed countries. Bad hygiene and poor health access are important risk factors for the high incidence and prevalence of this disease in under-developed regions. The present study was performed in a Hospital that attends disadvantaged patients and the present series included only men with low income and low education level. More often it manifests in middle aged men and forward, and in this series the epidemiologic data are coincident with those of literature (7).

In this series, the only histologic type was epidermoid carcinoma, and the literature appoints it as the most frequent subtype. Most patients presented pT2 stage tumors, which was the pathologic criteria for indication of lymphadenectomy for the included patients. This fact reflects that, even though this is an easily noted disease with a relative simple diagnosis, usually patients take a long time to seek medical help, increasing significantly morbidity of the disease and its treatments.

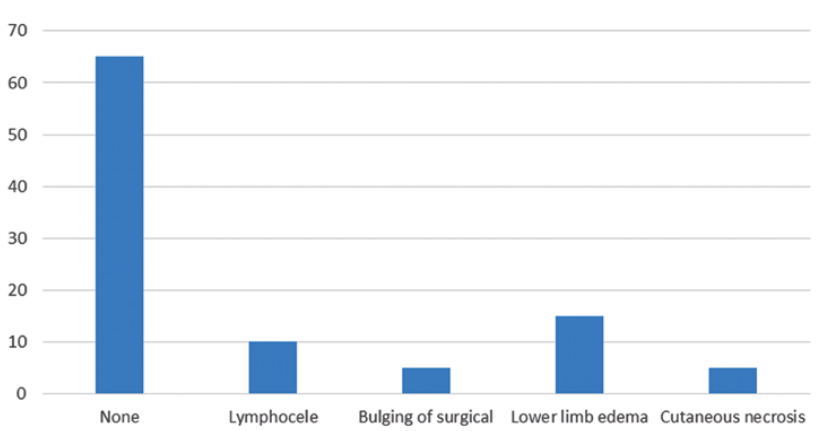
Since lymph node involvement is an important determining factor for mortality of this kind of tumor, IL must be performed even prophylactically. However, there are post-surgical complications, such as lymphedema, lymphocele, skin necrosis, deep venous thrombosis and thrombophlebitis, in 30 to 70% of patients submitted to IL (1, 2). VEIL main advantage in relation to IL is

Table 2 - Results of Analysis of Variance (ANOVA) to compare means and proportion in reference to the data of current study.

Variables	Current study	Romanelli P (6)	Pahwa HS (7)	Chaudhari R (12)	Kumar V (13)	Yuan JB (14)
Number of patients	11	20	10	14	20	12
Surgical mean time	85	119	144	194	97	92
P-value	Ref.	**0.038***	**0.023***	**0.015***	0.442	0.64
Skin complications (%)	10	6	0	0	6	4.2
P-value	Ref.	0.605	**<0.001***	**<0.001***	0.112	**0.0321***
Lymphatic complications (%)	25	27.2	20	27.2	30	12.5
P-value	Ref.	0.713	0.345	0.118	0.067	**0.039***
Intrasurgical complications	0	0	0	0	0	0
P-value	Ref.	-	-	-	-	-
Mean number of dissected lymph nodes	5.7	8	10.6	7.6	9.3	10.5
P-value	Ref.	0.456	**0.0267***	0.059	**0.038***	**0.0302***
Recurrence	2 in a mean follow-up of 28 months	2 in a mean follow up of 20 months	not discussed	0 in a mean follow-up of 48 months	0 in a mean follow-up of 16 months	not discussed
P-value	Ref.	0.901	-	0.623	0.0781	-

*Significant. Ref.: Reference for the test.
P-value: Error probability
Source:Author

Figure -1 Post-surgical complications following VEIL.



the reduction of morbidity. It is lower especially when related to skin (necrosis or post-surgical infection of surgical wound), and in several series these complications were not noted (8-11). General morbidity of VEIL varied from 20 (9, 10) to 33.2% (8), and lymphocele was the most frequent complication. Although VEIL has a significant morbidity rate, it is much lower than conventional IL. Pahwa et al., in a series of 10 patients, describes the incidence of infra-umbilical emphysema, that self-healed in 100% of patients. This was not observed in our patients (9). In that work, the incidence of positive lymph nodes was irrelevant, although the IL indication criteria were precise.

In this series of 20 VEIL, trans-surgical procedure was satisfactory in general, as the data presented in Table-2. The surgical time was excellent, statistically significant when compared to other series in literature (8, 9, 12), probably due to rapid proficiency gathered by the surgeons, that previously attended practical and theoretic courses, under the guidance of an experienced tutor. It seems that these specific VEIL courses are able to allow the reproducibility of the surgery with adequate safety.

Tobias-Machado (10) describes the mean surgical time of VEIL of 126 minutes versus 92 minutes of the conventional technique (11). However, it must be taken into account the learning curve of laparoscopy. In spite of the longer surgical time, the studies usually do not describe intra-operatory complications or conversions, and the longer surgical time is not a limiting factor for its use. There is a significant statistical difference in relation to the number of dissected lymph nodes, and in this series was lower than others in literature (9, 13, 14). This fact may be explained by the initial experience of the urologic department of our institution and with more procedures being performed, the results will equal to those of literature. A better understanding of superficial inguinal lymph node distribution will also contribute to a better lymph node dissection (15). Negligible bleeding and the lack of complications or conversions were also positive aspects of this initial series, reinforcing the safety of the procedure. Also, due the small size of the incision, VEIL has better cosmetic results. Therefore, patients are well satisfied with the results of the surgery, due to better cosmetics associated to lower morbidity (14).

Main complications of this series are summarized in Figure-1. Most frequently they were related to lymphatic drainage, including lower limb edema and lymphocele, minor complications that were conservatively treated. There was a significant statistical and unfavorable difference in relation to literature (14). The same was observed with other minor complications such as skin necrosis and bulging of surgical wound (9, 12, 14). We believe that all are related to the initial experience; therefore, proficiency is still not reached. With the inclusion of new patients, there will be a significant reduction of complications, approaching the results to the favorable number of literature.

Until nowadays, the bigger Latin-American study in literature included 20 patients submitted to 33 VEILS. 55% of patients were N0 and 45% N+. VEIL was performed bilaterally in 13 patients and 7 received unilateral VEIL associated to contra-lateral conventional IL. Mean surgical time was 119 minutes and the mean number of dissected lymph nodes was 8 by procedure. Global complication rate was 33.2%, and 27.2% were lymphatic. No patient showed cutaneous necrosis. In 6 patients whose internal saphenous vein was preserved, there was no lymphatic complications. Global survival time was 80% and cancer-specific survival was 90%, with a median follow-up of 20 months (8).

Recently, a European study compared the evolution of 33 VEIL versus 35 IL in 42 patients. Wound surgical complication rate was 6% in VEIL versus 68% in IL (p=0.0001). Also, patients submitted to VEIL had lower hospitalization time (4.9 days, p=0.0001). Other important aspects are the number of dissected lymph nodes and the number of positive lymph nodes, that was equal in both groups or slightly better in VEIL, that provided similar results but with a lower rate of post-surgical complications. Ho-

wever, in that study, as in others, the follow-up time was not long enough to propose an appropriate analysis of survival (13). The comparison of our results to other series is presented in Table-2.

Usually, patients die 2 years after diagnosis of primary lesion when not treated, due to major local and regional complications or development of metastasis in other organs (1). In our series, follow-up time was not ideal, mainly due to the low social and economic status of patients, that compromise awareness and commitment to treatment.

Although more than a decade has passed since the initial description of VEIL, there is still no study showing the applicability of this technique in small and medium size hospitals, therefore limiting its use to referral centers. The low number of patients, the retrospective aspect and the small follow-up time of our study precludes a more profound analysis of the oncologic safety of this technique. However, it was possible to demonstrate its use in small centers. Due to low incidence, multicenter studies are warranted to define the role of VEIL in the treatment of penile cancer, its oncologic safety and the potential use in other types of tumors.

CONCLUSIONS

The study presents a reproducible and easy surgery, however many patients submitted to VEIL in this series presented some kind of morbidity, although minor, especially related to lymphatic drainage. The number of dissected lymph nodes was lower than in other important literature series, probably due to the ongoing learning curve. VEIL seems to be an alternative to reduce post-surgical morbidity of IL, easy to perform and reproducible in median size centers. However, randomized prospective studies are necessary to prove superiority of VEIL and to define its role in the treatment of penile cancer.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Clinicopathological characteristics of surgically treated localized renal masses in patients previously exposed to chemotherapy

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ABSTRACT

Purpose: To explore the potential association between renal mass characteristics and a history of chemotherapy.
Materials and methods: A retrospective review of records of patients surgically treated for a localized renal mass between 2000 and 2012 was undertaken following an institutional review board approval. Patients age and sex, renal mass clinical characteristics (radiological size and mode of presentation) and pathological characteristics (diagnosis, renal cell carcinoma subtype, Fuhrman grade and stage) were compared between patients with and without a history of chemotherapy, using Fisher's exact test, Student's t-test and Wilcoxon rank sum test. A multivariate logistic analysis was performed to evaluate the independent association of chemotherapy and tumor pathology.
Results: Of the 1,038 eligible patients, 33 (3%) had a history of chemotherapy. The distribution of clinical stage, renal mass diagnosis, renal cell carcinoma subtype, Fuhrman grade, pathological stage, sex and median age were similar between the general population and the chemotherapy group. However, the latter had a higher rate of incidental presentation (P = 0.003) and a significantly smaller median radiological tumor size (P = 0.01). In a subset analysis of T1a renal cell carcinoma, the chemotherapy group presented an increased rate of high Fuhrman grade (P = 0.03). On multivariate analysis adjusted for radiological tumor size, sex and age the chemotherapy cohort had a 3.92 higher odds for high Fuhrman grade.
Conclusion: Patients with a history of chemotherapy typically present with smaller renal masses that, if malignant, have higher odds of harboring a high Fuhrman grade and thus may not be suitable for active surveillance.

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Keywords:
Carcinoma, Renal Cell; Chemotherapy, Cancer, Regional Perfusion; Kidney Neoplasms

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INTRODUCTION

In the US, kidney cancer affects approximately 63,990 new patients each year and causes the death of more than 14,000 on an annual basis (1). In the general population, the most frequent malignant histological subtype is the clear cell renal cell carcinoma followed by the papillary and chromophobe subtypes (2). However, the clinicopathological characteristics of renal masses and specifically of renal cell carcinoma have been shown to be different in specific subpopulations (3-5).

A positive medical history of chemotherapy has been associated with an increased risk of developing secondary malignancies including

kidney cancer (6-9). Still, the clinicopathological characteristics of renal masses in patients with a history of chemotherapy have yet to be described. Chemotherapeutic agents may affect the clinicopathological profile of renal masses through several mechanisms. The nephrotoxic effect that some chemotherapeutic agents have in the presence of additional insulting agents could lead to chronic renal damage (10, 11) that, can be associated with a higher prevalence of papillary renal cell carcinoma and better oncological outcomes (5). On the other hand, renal masses in patients with past chemotherapy exposure can also present a completely distinct and possibly a more aggressive clinicopathological profile due to the carcinogenic effect some chemotherapeutic agents may exert on renal cells (12). While most evidence on chemotherapeutic carcinogenicity is associated with hematologic malignancies, specific chromosomal translocations have been documented in renal masses in pediatric patients following chemotherapy (13).

In this study, we aim to describe the clinical and pathological characteristics of renal masses in individuals with a history of chemotherapy and compare them to those of the general population in order to assess if they require any special considerations when deciding on their management.

MATERIALS AND METHODS

Cohort

Following approval from the institutional review board, records of patients who underwent extirpative therapy for a localized renal mass at our institution between 2000 and 2012 were reviewed. Patients included in the study were those who underwent partial or radical nephrectomy for a renal mass. Patients treated with ablation, who had a hereditary syndrome such as Von Hippel - Lindau, or had a locally advanced mass were excluded from the study. The following variables were collected: age, sex, history of chemotherapy, mode of presentation (incidental vs. symptomatic), clinical stage, radiological size, pathological diagnosis (malignant vs. benign), renal cell carcinoma (RCC) subtype, Fuhrman grade and pathological stage.

Statistical analysis

Patient and renal mass characteristics were compared between patients with and without history of chemotherapy using Chi-square and Fisher's exact test for categorical data as well as Student's t-test and Wilcoxon rank sum test for continuous data as appropriate. In addition, a subgroup analysis compared patient and disease characteristics in a cohort of patients with small renal masses (SRM). The data are reported as median (interquartile range) or number (%). Finally, a multivariate logistic analysis was done in order to assess the association of medical history of chemotherapy and Fuhrman grade while accounting for confounding parameters (i.e. sex, age, malignant mass (RCC) radiological size). Fuhrman grade was categorized as low (1-2) and high (3-4). All tests were 2-tailed. $P < 0.05$ was considered statistically significant. Analyses were performed using the R v3.3.1 software (the R Foundation for Statistical Computing, Vienna, Austria) using "Hmisc" and "gmodels" libraries.

RESULTS

Of the 1,652 available records, 1.038 met the inclusion criteria and were reviewed. The cohort was predominantly male (59%) with a median age of 61 years. Only 33 (3%) patients of the total cohort had a positive medical history for chemotherapy. Patient and renal mass characteristics are detailed in Table-1. There was no significant difference in the distribution of sex ($p = 0.4$), clinical and pathological stage ($p = 0.4$ and 0.5 respectively), renal mass pathological diagnosis ($p = 1$), RCC subtype ($p = 1$) and Fuhrman grade ($p = 0.09$). However, renal masses in patients with a medical history of chemotherapy were more frequently diagnosed incidentally (97% vs. 77%, $p = 0.003$) and demonstrated a significantly smaller median radiological size (3.1 vs. 4cm , $p = 0.01$).

When renal mass and patient characteristics were compared in the subgroup of patients with SRM, median radiological size remained significantly different between those who underwent

Table1 - Patient and renal mass characteristics in the total cohort.

Variable	Total	Chemo+	Chemo-	P value
Number of patients	1038	33 (3%)	1005 (97%)	
Gender				**0.4**
Male	617 (59%)	17 (52%)	600 (60%)	
Female	421 (41%)	16 (48%)	405 (40%)	
Median Age (IQR)	61 (52-68)	63 (56-66)	60 (52-68)	0.4
Mode of presentation				**0.003**
Incidental*	801 (77%)	32 (97%)	769 (77%)	
Symptomatic	237 (23%)	1 (3%)	236 (23%)	
Median radiological size in cm	4 (2.7-6.5)	3.1 (1.8-4.9)	4 (2.7-6.6)	0.01
Clinical Stage				**0.4**
T1a	540 (52%)	20 (61%)	520 (52%)	
T1b	275 (26%)	10 (30%)	265 (26%)	
T2a	120 (12%)	2 (6%)	118 (12%)	
T2b	103 (10%)	1 (3%)	102 (10%)	
Renal mass diagnosis				**1**
Benign	187 (18%)	6 (18%)	181 (18%)	
Malignant	851 (82%)	27 (82%)	824 (82%)	
RCC subtype				**1**
Clear Cell	631 (74%)	22 (81%)	609 (74%)	
Papillary	180 (21%)	5 (19%)	175 (21%)	
Chromophobe	23 (3%)	0 (0%)	23 (3%)	
Other	17 (2%)	0 (0%)	17 (2%)	
Fuhrman grade				**0.09**
1	166 (20%)	3 (11%)	163 (20%)	
2	492 (58%)	14 (52%)	478 (58%)	
3	151 (18%)	6 (22%)	145 (18%)	
4	42 (5%)	4 (15%)	38 (5%)	
Pathological stage				**0.5**
T1a	406 (48%)	13 (48%)	393 (48%)	
T1b	189 (22%)	9 (33%)	180 (22%)	
T2a	59 (7%)	0 (0%)	59 (7%)	
T2b	39 (5%)	1 (4%)	38 (5%)	
≥ T3	158 (19%)	4 (15%)	154 (19%)	

*Incidental presentation includes patients that were found to have a renal mass during follow-up visits (3 of those with positive history of chemotherapy).

chemotherapy in the past and those who did not (2 vs. 2.8cm, p = 0.009) (Table-2). On the other hand, the distribution of the mode of presentation was similar between the two patient groups as well as the median age and the distribution of sex, renal mass diagnosis, RCC subtype and pathological stage (p = 0.3, 0.9, 0.6, 1, 0.9, 0.2 respectively). Interestingly, in the SRM subgroup, Fuhrman grade distribution was revealed to be different with higher rates of high Fuhrman grade in the chemotherapy group

Table 2 - Patient and renal mass characteristics in the SRM cohort.

Variable	Total	Chemo+	Chemo-	P value
Number of patients	540	20 (4%)	520 (96%)	
Gender				**0.6**
Male	248 (59%)	8 (50%)	240 (59%)	
Female	175 (41%)	8 (50%)	167 (41%)	
Median Age (IQR)	60 (51-68)	62 (54.5-65.3)	59.5 (51-68)	0.9
Mode of presentation				**0.3**
Incidental*	483 (89%)	20 (100%)	463 (89%)	
Symptomatic	57 (11%)	0 (0%)	57 (11%)	
Median radiological size in all SRM in cm (IQR)	2.7 (2-3.2)	2 (1.7-2.7)	2.8 (2-3.3)	0.009
Median radiological size in malignant SRM in cm (IQR)	2.8 (2-3.3)	1.8 (1.7-2.7)	2.8 (2.1-3.3)	0.006
Renal mass diagnosis				**1**
Benign	117 (22%)	4 (20%)	113 (22%)	
Malignant	423 (78%)	16 (80%)	407 (78%)	
RCC subtype				**0.9**
Clear Cell	305 (72%)	13 (81%)	292 (72%)	
Papillary	100 (24%)	3 (19%)	97 (24%)	
Chromophobe	10 (2%)	0 (0%)	10 (2%)	
Other	8 (2%)	0 (0%)	8 (2%)	
Fuhrman grade				**0.0001**
1	116 (27%)	1 (6%)	115 (28%)	
2	255 (60%)	10 (62%)	245 (60%)	
3	48 (11%)	2 (12%)	46 (11%)	
4	4 (1%)	3 (19%)	1 (0%)	
Dichotomized Fuhrman grade:				
Low (1-2)	371 (88%)	11 (69%)	360 (88%)	0.03
High (3-4)	52 (12%)	5 (31%)	47 (12%)	
Pathological stage				**0.2**
T1a	372 (88%)	12 (75%)	360 (88%)	
T1b	21 (5%)	2 (12%)	19 (5%)	
T2a	2 (0%)	0 (0%)	2 (0%)	
T2b	0 (0%)	0 (0%)	0 (0%)	
≥ T3	28 (7%)	2 (12%)	26 (6%)	

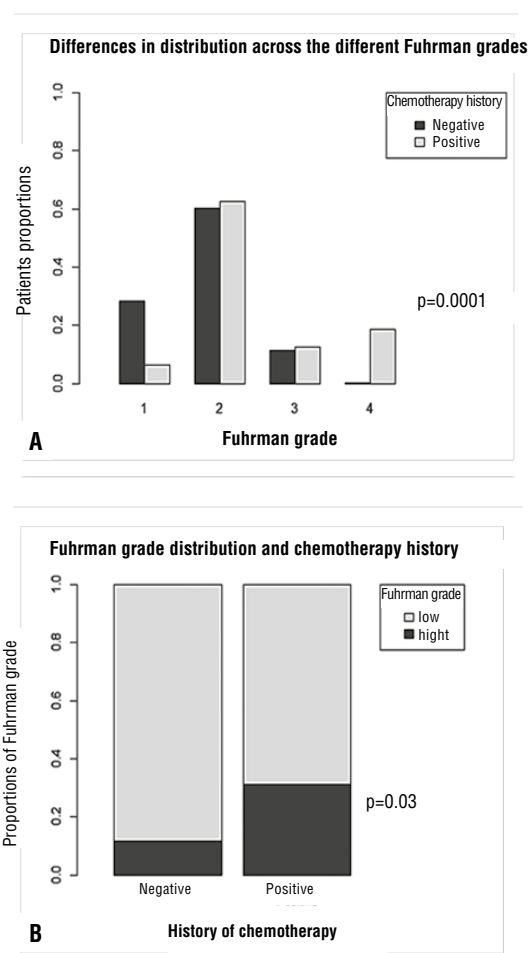
*Incidental presentation includes patients that were found to have a renal mass during follow-up visits (3 of those with positive history of chemotherapy).

(31% vs. 12%, p = 0.03) (Figures 1a-b). In the multivariate analysis that aimed to evaluate whether a history of chemotherapy remains significantly associated with Fuhrman grade when adjusting for known confounders (i.e sex, age, renal mass radiological size), patients with RCC and a history of chemotherapy had 3.92 (CI 1.16-11.71, p = 0.02) higher odds of harboring a high Fuhrman grade (Table-3).

DISCUSSION

Fung et al. and van den Beit-Dusebout et al. described an increased risk for the development of secondary malignancies, in particular hematologic malignancies after chemotherapy with a median latency of 12.5 and 17.6 years respectively (7, 9). It has also been reported that chemotherapy increases the risk of renal cancer in childhood cancer survivors (7, 14). The effect of chemotherapy on the clinicopathological characteristics of renal masses has yet to be reported. In this study, we aimed to evaluate whether patients with a previous exposure to chemotherapy may present with a renal mass that is clinically and pathologically different from those in the general population.

Figure 1 - The distribution of Fuhrman grade was significantly different between the chemotherapy group and the general population (1a). The chemotherapy group had significantly higher rates of high Fuhrman grade (1b).



This study's cohort included only 33 (3%) patients with a history of chemotherapy surgically treated for a localized renal mass at our institution. While most of the patients and renal mass characteristics that the chemotherapy group presented did not differ from those of the general population, some peculiarities were noticed. Renal masses in patients who were exposed to chemotherapy in the past were more frequently diagnosed incidentally. Moreover, their median radiological size was significantly smaller. These findings are not surprising since patients with a history of chemotherapy are under surveillance for their primary malignancy and thus, undergo imaging tests more frequently than the general population. In fact, the rising incidence of renal masses is considered to be partly due to the increase in cross sectional imaging (15, 16).

Interestingly, when renal mass and patient characteristics were compared in only the SRM cohort it was noticed that patients with a history of chemotherapy still presented with significantly smaller masses. Furthermore, when only malignant SRMs were examined, these were characterized by a higher rate of high Fuhrman grade, which is known to be independently associated with RCC biological behavior (17, 18). Current literature is lacking in evidence that could explain the study's findings. However, studies that explored the development of secondary malignancies following chemotherapy report an increased risk of kidney cancer following platinum-based therapy (7). Renal cells may be affected by the toxicity of platinum-based chemotherapies due to their exposure. In fact, the kidney is the primary means for short and long-term cisplatin excretion (19).

Table 3 - Multivariable analyses to evaluate the association of Fuhrman grade and a history of chemotherapy in localized RCC, adjusted for age, sex and radiological size.

Factor	OR (95% CI)	P value
History of chemotherapy		0.02
No	Reference	
Yes	3.92 (1.16-11.71)	
Radiological size in cm	1.25 (0.85-1.85)	0.2
Sex		0.1
Female	Reference	
Male	1.11 (0.61-2.04)	
Age	1.02 (1.00-1.05)	0.1

In addition, studies have described the persistence of partially reactive circulating platinum even after 10 years following completion of chemotherapy (20, 21) and have documented the presence of platinum-DNA adducts in different human tissues including the kidney (21, 22) that could contribute to the different pathological profile that RCC demonstrates in patients with a history of chemotherapy. In this study, platinum-based chemotherapeutic agents were used in about a third of the chemotherapy cohort patients (Table-4). Other chemotherapeutics that these patients were exposed to included alkylating agents (Lomustine and Cyclophosphamide) and topoisomerase II inhibitors (Etoposide) that are known to contribute to the development of secondary malignancies (23, 24). However, none of these chemotherapeutics was shown to be associated with the pathological characteristics of renal masses.

There are several limitations to this study that need to be acknowledged. First, selection bias may be present due to the retrospective nature of the study. In addition, the study is based on a cohort treated at a referral center and thus, this study's findings may not be extrapolated to other populations. Extrapolation of the findings to the general population may also be difficult due to the limited number of patients with a history of chemotherapy used in the analysis. Since the chemotherapy group only included 33 patients with different primary malignancies and treatment plans, confounding factors such as the type of chemotherapeutic agents, dosage used, and time from chemotherapy to renal mass diagnosis could not be accounted for. Also, due to the cohort size there was an insufficient power to evaluate how the study's findings correlate to the oncological control of malignant SRMs in patients with a history or chemotherapy. Despite these limitations, our study provides initial evidence on the possible association between medical history of chemotherapy and the biological characteristics of RCC in the context of SRM. Clinically, the study's findings may indicate that patients with a history of chemotherapy may not be the ideal candidates for active surveillance since they have higher odds for a disease that is histologically more aggressive. Further studies are necessary in order to clarify the impact of past exposure to chemotherapy on the survival of patients managed with active surveillance for their SRM.

CONCLUSIONS

In this study, a history of chemotherapy was associated with renal masses that were more frequently incidental and of smaller radiological size. In addition, in the SRM subset chemotherapy was significantly associated with high Fuhrman grade. Additional studies are necessary in order to

Table 4 - Primary malignancies and chemotherapy characteristics.

	Rate (Percentage) / Median(IQR)
Primary Malignancy:	
Anal squamous cell carcinoma	1 (3%)
Lymphoma*	5 (15%)
Breast	10 (30%)
Cervical carcinoma	1 (3%)
Cholangiocarcinoma	1 (3%)
Colon	3 (9%)
Esophageal carcinoma	1 (3%)
Fallopian tube carcinoma	1 (3%)
Glioblastoma	1 (3%)
Lung carcinoid	1 (3%)
Lung carcinoma	4 (12%)
Tongue squamous cell carcinoma	1 (3%)
TCC	2 (6%)
Unknown origin	1 (3%)
Combined chemotherapy with radiotherapy	7 (21%)
Median number of years from chemotherapy to surgery	3 (2-11)
Platinum based chemotherapy	
Yes	12 (36.4%)
No	14 (42.4%)
Unknown	7 (21.2%)
Total	**33**

*Lymphoma includes: Hodgkin and non-Hodgkin lymphoma

clarify the biological mechanisms through which chemotherapy may contribute to the more aggressive profile of T1a RCC. Furthermore, future studies are required in order to examine how chemotherapy may have a role in survival outcomes of patients with localized RCC.

ABBREVIATIONS

RCC = Renal Cell Carcinoma
SRM = Small Renal Mass

CONFLICT OF INTEREST

None declared.

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Effect of vitamin D supplementation on 24-hour urine calcium in patients with calcium Urolithiasis and vitamin D deficiency

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ABSTRACT

Purpose: Hypercalciuria is one of the risk factors for calcium kidney stone formation (the most common type of urinary stones). Although vitamin D deficiency is prevalent among urolithiasis patients, the effect of vitamin D supplementation on urine calcium in these patients is still unclear.

Materials and Methods: In this retrospective study, medical and laboratory tests records of 26 patients with recurrent calcium kidney stones and vitamin D deficiency treated with 50000IU vitamin D per week for 8-12 weeks were analyzed. The changes in 24-hour urine calcium (24-h Ca), serum 25-hydroxyvitamin D (25 (OH) D), serum parathormone (PTH), other 24-hour urine metabolites and calculated relative supersaturations of calcium oxalate (CaOxSS), calcium phosphate (CaPSS) and uric acid (UASS) were assessed. Moreover, correlations between changes in 24-h Ca and other aforementioned variables were assessed.

Results: Serum 25 (OH) D and 24-h Ca increased after vitamin D supplementation, while serum PTH decreased ($p < 0.001$, for all analyses). The levels of 24-hour urine sodium and urea increased significantly ($p = 0.005$ and $p = 0.031$, respectively). The levels of CaOxSS and CaPSS increased, but the changes were not significant ($p = 0.177$, and $p = 0.218$, respectively). There were no correlations between the changes in 24-h Ca and serum 25 (OH) D or PTH.

Conclusions: The result of current study suggests that although urine Ca increased in vitamin D supplemented patients, this increase was not associated with the increase in serum vitamin D and may be due to other factors such as dietary factors. Further randomized clinical trials considering other factors associated with urine Ca are warranted.

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INTRODUCTION

The urinary stone disease is a common disease with a high risk of recurrence and increasing prevalence around the World (1). Calcium (Ca) stones are the most common type of urinary stones in many countries, including Iran (2). Hypercalciuria is the most common risk factor for Ca kidney stone in many countries (3). Many factors including non-dietary and dietary factors are shown to cause hypercalciuria; however, the exact impact of some of these factors on urinary Ca excretion is still unclear (4).

Vitamin D deficiency is one of the most common health problems all over the World. Studies have shown a high prevalence of moderate to severe vitamin D deficiency in various cities of Iran (5). Because of the essential role of vitamin D in Ca homeostasis and bone health, as well as its role in different chronic diseases (6, 7), many guidelines emphasize the importance of treating vitamin D deficiency (8, 9).

According to current studies, vitamin D deficiency is prevalent among patients with kidney stones (10-12). However, the treatment of vitamin D deficiency in kidney stone patients is a matter of debate (13), according to the high prevalence of osteoporosis and low bone density (14), and the limited and conflicting results regarding the effect of vitamin D supplementation on the risk of developing hypercalciuria in patients with kidney lithiasis.

The current study aims to evaluate the effect of vitamin D supplementation on 24-hour urine Ca in a group of patients with recurrent Ca kidney stones and vitamin D deficiency.

MATERIALS AND METHODS

Study Design and patients

In this retrospective study, the medical records of patients referred to the Stone Prevention Clinic of Labbafinejad Hospital, Tehran, Iran, in recent two years (December 2015 to December 2017) were reviewed. Patients with history of recurrent kidney stones (with a history of at least two radiopaque stone episodes) (15) and vitamin D deficiency [serum 25 hydroxyvitamin D (25 (OH) D) below 30ng / mL] who were treated with 50000IU vitamin D per week for 8-12 weeks, according to patient's demographic and anthropometric data (8), were enrolled. Other inclusion criteria were baseline 24-hour urine Ca below 300mg / 24hrs; age over 18 years and existence of valid data of serum 25 (OH) D and 24-hour urinary analysis before and after vitamin D supplementation. Participants were excluded if they meet at least one of the following criteria: known history of diabetes mellitus; primary hyperparathyroidism; malignancy or malabsorption; any disease that affects serum 25 (OH) D and Ca or 24-hour urine Ca (such as sarcoidosis and some other chronic granulomatous disorders); using other forms of vitamin D supplement (lower doses or intramuscular) during the treatment period; changes in dosage or new addition of thiazide diuretics, or any drug which may affect serum or urine Ca during the treatment period (such as lithium); taking Ca supplements; history of vitamin D supplementation (oral or intramuscular) three months prior to study; 24-hour urine under-collection (24-hour urine creatinine (Cr) > 800mg for men and > 600mg for women (16)); and pregnancy or lactation. All patients received nutritional advice for the prevention of kidney stone according to European Association of Urology (EAU) guideline (17).

Study outcomes and laboratory tests

Patient information such as demographic and anthropometric data, past medical and drug history had been collected by physicians of Stone Prevention Clinic of Labbafinejad Hospital, as previously described (18).

Fasting blood samples were taken from patients and blood serums were separated for the analyses. The 24-hour urine samples were collected with hydrochloric acid 6N as the preservative. Serum 25 (OH) D and parathormone (PTH) were measured by the electrochemiluminescent method (Elecsys 2010 automatic analyzer, Roche Hitachi). Serum or urine urea, Cr, Ca, phosphorous, sodium (Na), potassium, uric acid, magnesium (Mg), citrate (Cit) and oxalate (Ox) concentrations were analyzed as reported previously (19). Relative Supersaturations of CaOx (CaOxSS), Ca phosphate (CaPSS) and uric acid (UASS) were calculated using LithoRisk software (Biohealth, Italy) (20), using measured 24-hour urine metabolites.

Statistical analyses

All data analyses were performed using SPSS version 23. Normality of data was checked by Shapiro Wilk test and Q-Q plot. Within-group differences were assessed by a Paired-Samples T test (for normally distributed continuous data) and Wilcoxon signed-rank test (for Skewed continuous data). Correlations between changes in 24-h Ca (24-h Ca diff) and changes in serum 25 (OH) D (25

(OH) D diff), changes in serum PTH (PTH diff) and changes in other 24-hour urine metabolites were assessed. Pearson correlation coefficient was used for normally distributed continuous data and Spearman correlation coefficient was used for skewed continuous data. The level of significance was set at p-value < 0.05.

RESULTS

From 334 kidney stone patients who were treated for vitamin D deficiency at the time of the study, 26 met the inclusion and exclusion criteria and enrolled in the analyses. The most common reason for exclusion was taking a thiazide diuretic. Baseline characteristics of patients are shown in Table-1. The majority of participants had serum 25 (OH) D in the range of 10-19ng / mL. Seven patients (26.9%) had baseline hyperparathyroidism (PTH > 65pg / mL).

Urine and serum parameters before and after vitamin D supplementation (median follow-up period of 4.12 months) are shown in Table-2. The mean level of serum 25 (OH) D increased significantly after vitamin D supplementation (p < 0.001). A detailed overview showed that the level of 25 (OH) D did not increase in 2 patients (7.7%) and did not reach the normal levels (> 30) in 9 patients (34.6%). The level of 24-h Ca increased and the level of serum PTH decreased significantly after vitamin D supplementation (p < 0.001, for both analyses). Considering other 24-hour urine metabolites, the levels of 24-hour urine Na (24-h Na) and Urea (24-h Urea) increased significantly (p = 0.005 and p = 0.031, respectively). The levels of CaOxSS and CaPSS also increased, but the changes were not significant (p = 0.177, and p = 0.218, respectively) (Table-2).

Table 1 - Baseline characteristics of recurrent calcium stone patients with vitamin D deficiency. All values are mean (SD) unless otherwise mentioned.

	Value
Gender (male%)	20 (76.9%)
Age (years)	47.5 (12.31)
BMI [a] (kg / m^2)	28.00 (5.13)
Follow-up period (month) [median (IQR)]	4.12 (2.20)
Serum BUN [b] (mg / dL)	14.58 (3.42)
Serum Creatinine (mg / dL)	1.15 (0.14)
Serum calcium (mg / dL)	9.65 (0.45)
Serum phosphorus (mg / dL)	3.26 (0.58)
25-hydroxyvitamin D (ng / mL) n (%)	
0-9	6 (23.1%)
10-19	15 (57.7%)
20-25	5 (19.2%)
PTH [c] (pg / mL) n (%)	
< 65	19 (73.1)
≥ 65	7 (26.9)

[a] = Body Mass Index; [b] = Blood Urea Nitrogen; [c] = Parathormone

The correlation between 24-h Ca diff and changes in other variables were assessed. There was no correlation between 24-h Ca diff and baseline serum 25 (OH) D level (r = 0.175, p = 0.392), 25 (OH) D diff (r = -0.069, p = 0.738), or PTH diff (r = 0.038, p = 0.879) (Figure-1). Moreover, there was no correlation between 24-h Ca diff and the changes in 24-h Na (24-h Na diff) (r = 0.186, p = 0.362), changes in 24-h Urea (24-h Urea diff) (r = 0.097, p = 0.693) or changes in other variables.

DISCUSSION

The results of the current study indicate that, although urine Ca increased in vitamin D supplemented patients, this increase was not associated with the increase in serum vitamin D. There are limited trials, which assessed the effect of vitamin D supplementation on urine Ca in patients with kidney stones. To the best of our knowledge, only three studies had evaluated this effect (21-23). In a study by Leaf et al. (21), 29 patients with renal stones received 50.000IU vitamin D per week for eight consecutive weeks. In a study by Ferroni et al. (22), patients received either 1.000IU vitamin D daily (n = 8) or 50.000IU vitamin D per week (n = 13) for 6 weeks. Finally, Hesswani et al. (23) retrospectively evaluated 34 patients with renal stones, which were treated with a median intake of 1.000IU vitamin D, and 945mg Ca supplements simultaneously. The median time of follow-up was 39 months. The only study that re-

Table 2 - Urine and serum parameters before and after vitamin D supplement therapy. All values are mean (SD) and p-value stands for the paired t-test unless otherwise mentioned.

	Before	After	P value
25 (OH)D (ng / mL) (n = 26)	14.08 (5.49)	33.64 (13.89)	< 0.001***
Serum PTH (pg / mL) (n = 19)	55.89 (21.93)	38.42 (15.39)	< 0.001***
Serum Ca (mg / dL) (n = 18)	9.66 (0.44)	9.74 (0.35)	0.537
24-hour urine Ca (mg / day) (n = 26)	149.92 (78.61)	229.92 (104.83)	< 0.001***
24-hour urine Na (mEq / day) (n = 26)	133.89 (51.37)	171.08 (54.65)	0.005**
24-hour urine Urea (gr / day) (n = 19)	22.97 (8.03)	28.74 (12.19)	0.031*
24-hour urine UA (mg / day) (n = 26)	413.67 (135.22)	455.35 (194.15)	0.357
24-hour urine P (gr / day) † (n = 26)	0.71 (0.30)	0.78 (0.36)	0.08
24-hour urine K (mEq / day) † (n = 26)	50.58 (20.80)	60.66 (29.27)	0.027*
24-hour urine OX (mg / day) (n = 26)	34.74 (17.68)	36.63 (17.54)	0.705
24-hour urine Cit (mg / day) (n = 26)	534.5 (252.2)	517.2 (281.4)	0.715
24-hour urine Mg (mg / day) † (n = 26)	78.08 (37.72)	113.08 (50.52)	0.003**
24-hour urine Cr (mg / day) (n = 26)	1.23 (0.46)	1.28 (0.44)	0.156
24-hour volume (mL) † (n = 26)	2000.6 (883.7)	2190.4 (791.6)	0.306
CaOX supersaturation (n = 26)	4.675 (2.652)	5.394 (3.202)	0.177
CaP supersaturation † (n = 26)	0.332 (0.297)	0.568 (0.722)	0.218
UA supersaturation (n = 26)	1.213 (0.922)	1.155 (0.860)	0.765

25 (OH) D = 25-hydroxyvitamin D; PTH = parathormone; Ca = calcium; Na = sodium; UA = uric acid; P = phosphorus; K = potassium; Ox = oxalate; Cit = citrate; Mg = magnesium; Cr = creatinine; CaOx = calcium oxalate; CaP = calcium phosphate

† P value stands for Wilcoxon signed-rank test

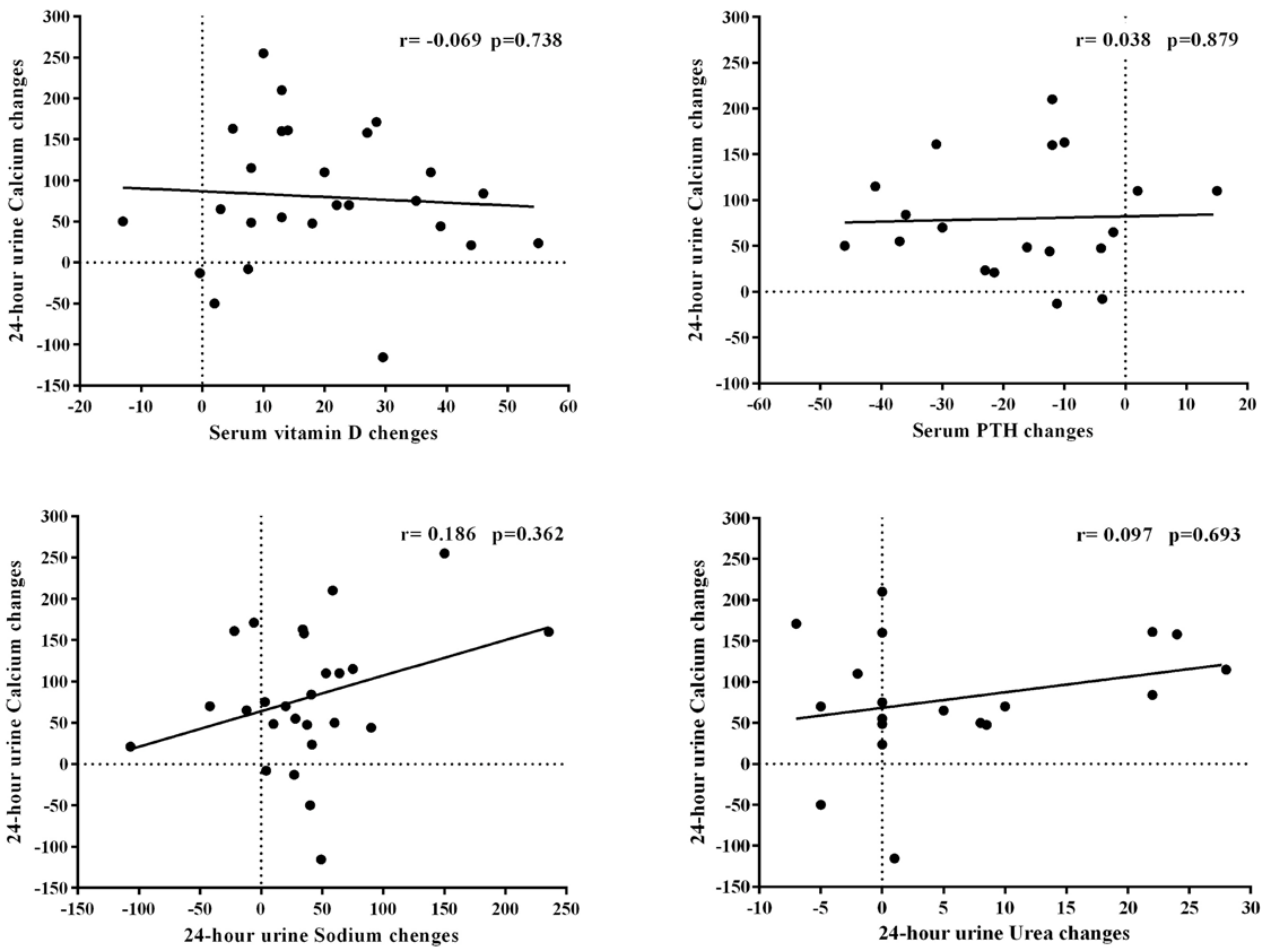
* p<0.05; ** p<0.01; *** p<0.001

ported an increase in urinary Ca was the study by Hesswani et al., in which patient received vitamin D and Ca co-supplements. However, in line with our results, there was no correlation between the changes in urinary Ca and changes in serum vitamin D in the study by Hesswani et al. The authors conclude that simultaneous consumption of Ca supplement may be a cause of urinary Ca increase. A meta-analysis by Malihi et al. (24) studied the effect of vitamin D and Ca co-supplementation in elderly patients or different diseases other than urolithiasis. Their results showed that long-term vitamin D supplementation (a minimum supplementation period of 24 weeks) increased the risk of hypercalciuria, and the risk was not modified by Ca co-supplementation (24).

Another finding of our study was that although urinary Ca levels increased significantly, the risk of stone formation, which was assessed by CaOx SS and CaPSS, did not increase significantly. This is in line with the finding of Malihi et al. that although vitamin D supplementation increased the risk of hypercalciuria, it did not increase the risk of kidney stone formation (24). It should be kept in mind that a variety of urinary constituents may affect urine relative supersaturation (25). Thus, even if Ca rises because of vitamin D supplement, urine supersaturation could be normalized by increasing other inhibitor metabolites, such as Mg and Cit. Additional clinical trials on patients with lithiasis are needed to assess this finding.

Urine Ca is associated with different variables including dietary intake. Different dietary factors including a high intake of animal protein (26), Na (27, 28) and sucrose (17) could increase urine Ca. Our results showed that the level of urine Na (as a surrogate for Na intake) (16) and urea (as a surrogate

Figure 1 - The correlation between the changes in 24-hour urine calcium (24-h Ca) and the changes in serum 25 (OH) D, serum PTH, 24-hour urine sodium (24-h Na) and urea (24-h Urea).



for total protein intake) (26) increased simultaneously after vitamin D supplementation. Although there was no correlation between 24-h Na diff, 24-h Urea diff and 24-h Ca diff and, the simultaneous increase of Na and urea could be the cause for urine Ca increase. Moreover, other dietary factors, which could affect urine Ca, were not assessed in our study. Multivariate analyses of large clinical trials considering other confounding factors such as dietary information of patients could elucidate this effect.

The significant decrease in serum PTH was another noteworthy finding in our study. PTH is a hormone that regulates serum Ca levels through several different mechanisms, including increasing Ca reabsorption in renal tubules and mobilizing Ca from bones, which result in decreased bone density (8). The level of serum PTH rises in patients with vitamin D deficiency and should be decreased with vitamin D supplementation (8). Some references consider PTH reduction to be one of the targets for treating vitamin D deficiency (29). The significant decline of PTH in the current study could show the adequacy of vitamin D supplementation in our study. The changes in PTH were measured in studies by Leaf et al. (21) and Hesswani et al. (23). Interestingly, none of these two studies reported a significant change in serum PTH. As mentioned by the authors, the lack of PTH suppression could be due to inadequate changes in serum vitamin D levels after supplementation (23). The decrease in serum PTH may increase urinary Ca because of decreasing Ca reabsorption in renal tubules. However, our results

did not show any correlation between urine Ca and serum PTH changes.

The response of serum PTH to vitamin D supplementation could be affected by different other factors such as Ca intake (30). Increasing Ca intake through diet or combined supplementation could increase PTH response, because PTH may not be suppressed without sufficient Ca intakes. All patients with recurrent calcium kidney stones should be advised to take 1000 to 1200mg of Ca per day through diet according to EAU guidelines (17), thus the significant change of PTH may be due in part to patient's sufficient Ca intake. However, we could not come to this conclusion due to the lack of calcium intake information. Undoubtedly, this should be assessed in other studies with dietary intake assessment.

Limitation of the current study, in addition to being retrospective, is the lack of control group, the possibility of over-collection, and the lack of data regarding dietary intakes of patients. However, the study had strict exclusion criteria including changes in dosage or new addition of thiazide diuretics, to rule out other factors, which may affect urinary Ca. Moreover, the study population was largely male which may reduce the generalizability of the results.

CONCLUSIONS

In conclusion, the results of the current study suggest that although urine Ca increased in vitamin D supplemented patients, this increase was not associated with the increase in serum vitamin D, but may be secondary to other factors such as dietary Na intake. Further randomized clinical trials considering other factors associated with urine Ca, such as dietary intake of patients, are warranted.

ABBREVIATIONS

Ca = Calcium
25 (OH) D = 25 hydroxyvitamin D
EAU = European Association of Urology
PTH = parathormone
Cr = creatinine
Na = sodium
Mg = magnesium
Cit = citrate
Ox = oxalate
CaOxSS = Supersaturations of CaOx
CaPSS = Supersaturations of Ca phosphate
UASS = Supersaturations of uric acid
24-h Ca = 24-hour urine Ca
24-h Ca diff = Changes in 24-h Ca
25(OH)D diff = Changes in serum 25 (OH) D
PTH diff = Changes in serum PTH
24-h Na = 24-hour urine Na
24-h Urea = 24-hour urine Urea
24-h Na diff = Changes in 24-h Na
24-h Urea diff = Changes in 24-h Urea

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Antibiotic prophylaxis prior to urodynamic study in patients with traumatic spinal cord injury. Is there an indication?

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ABSTRACT

Study design: Retrospective cohort of patients with traumatic spinal cord injury (SCI) that have been hospitalized for physical-functional rehabilitation purposes.
Objectives: To compare the incidence of urinary tract infection (UTI) after urodynamic study (UDS) in three hospitals that adopted different protocols with regard to the preparation of patients.
Setting: Sarah Network of Rehabilitation Hospitals, Brazil.
Materials and Methods: Between 2014 and 2015, 661 patients from three units of the same hospital network, one of which does not use antimicrobial prophylaxis independently of urine culture results, were evaluated after having undergone UDS. The results were compared in both univariate and multivariate analyses (logistic regression).
Results: The global rate of UTI after UDS was that of 3.18% (IC 95% 2.1-4.8), with no differences between the units. In the univariate analysis the only variable that was associated with UTI after UDS was that of T6 injuries or above (P = 0.029). The logistic regression has confirmed this result, with an adjusted odds ratio of 3.06 (IC 95% 1.01 to 9.26; P = 0.0476). The use of antimicrobial prophylaxis did not alter that risk.
Conclusions: This study has demonstrated that the use of antimicrobials does not prevent UTI after UDS. Patients with T6 traumatic SCI or above have got three times more chance of developing UTI after UDS if compared to those with a T7 injury or below, independently of the use of antimicrobials. Even in these patients the use of antimicrobials would not be justified.

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INTRODUCTION

The traumatic spinal cord injury (SCI) generates a high socio-economic impact, since it usually focuses on individuals in their productive phases, who start to demand constant medical attention for the rest of their lives (1). Independently of the level of the injury, these patients very often present neurogenic bladder dysfunction, with the necessity of frequent urologic exams, notedly urodynamic study (UDS). This exam is safe and has a low potential of causing bacteremia. On the other hand, these patients frequently empty their bladders with the aid of a clean intermittent catheteri-

zation (CIC), which usually leads them to develop asymptomatic bacteriuria (1).

Bacterial resistance to antimicrobials is a public health problem worldwide. Its main cause is the indiscriminate prescription of antimicrobials, which calls our attention to the importance of a constant review in prescription policies (2, 3). Patients with SCI are more susceptible to recurrent urinary tract infection (UTI) and / or vesical colonization by multiresistant germs (4).

Although a sole clinical trial suggests the use of prophylactic antimicrobials prior to UDS (5), there are still controversies with regard to the indication or not of its routine usage by such patients. Since we count on the fact that we have conducted UDS in patients with SCI from three units of a same hospital network, each following its own protocols, the efficacy of such protocols was analyzed before the UDS. We have considered the incidence of UTI as the primary outcome, and, as independent variables, apart from the participant hospital units, characteristics related with the individual and with the SCI.

MATERIALS AND METHODS

Between January, 2014, and December, 2015, three units of the Sarah Network of Rehabilitation Hospitals, Brazil, which adopted different routine protocols before UDS, were considered. The protocols were authorized by each unit's respective hospital-acquired infection committees. The delineation of this investigation is, thus, typical of a retrospective cohort, with no interference with the patient's preparation routine. The investigation project was submitted to the Ethics Committee of the Sarah Network, which approved it with no restrictions.

Six hundred and sixty one subsequent patients with traumatic SCI were analyzed, 197 (29.8%) of which came from the São Luis unit (henceforth called Hospital A), 328 (49.6%) from the Salvador unit (B) and 136 (20.6%) from the Brasilia unit (C). All the patients were hospitalized and participated in the rehabilitation program, which had an average duration of 30 to 45 days. All the data were collected, retrospectively, based on the information obtained from the electronic medical records and evaluation protocols of each respective hospital. We have considered as independent variables, apart from the unit where the UDS was conducted, the result of the basal urine culture, the sex and age of the patient, the level and age of the injury, the American Spinal Injury Association classification (ASIA), the presence of spasticity and the order of the exam (first or second). None of the patients has taken part more than once in the analysis.

Prior to the UDS, information concerning all the patient's urine and urine culture were collected. Patients with skin lesions, UTI and indwelling catheterization were excluded from the analysis, as well as outpatients, due to the difficulty in clinical observation. A culture was considered positive whenever any kind of bacterial growth was detected. In addition, the development of symptoms up to five days after the UDS, along with a new positive urine culture, were considered as UTI. Amongst the symptoms of UTI, we have considered malodor, macroscopic alterations, increases in urinary incontinence, dysuria (in patients with incomplete injuries), increases in spasticity, aggravations in the neuropathic pain, malaise, autonomic dysreflexia or fever with no other apparent cause (6).

In short, the protocols of the units involved consisted of:

- Hospital A: patients with a positive urine culture are submitted to antibiotic prophylaxis based on the urine culture, in a single dose, one hour before the UDS, while those with a negative urine culture receive 100 mg of nitrofurantoin.
- Hospital B: none of the patients is submitted to antibiotic prophylaxis before the UDS, independently of the result of the urine culture (positive or negative).
- Hospital C: patients with a positive urine culture are submitted to antibiotic prophylaxis based on the urine culture, in a single dose, two hours before the UDS, while those with a negative urine culture do not get prophylactic antibiotics.

In all of the three units, the UDS was carried out by professionals trained inside the Sarah Network, according to the ICS standards (7).

The data collected were compiled in the application Microsoft Excel. For the statistical analysis of proportions we used the chi-squared distribution study, while for the analysis of continuous variables we applied the Kruskal-Wallis test. The cutting criterion to consider a variable in the multivariate analysis was that of $P < 0.10$. The binary logistic regression analysis was carried out through the stepwise method (forward selection) with the aid of the application SPSS (version 17). The logistic model has allowed for an estimate of the probability of occurrence of UTI after the UDS, based on the presence of risk factors included in the analysis. The evaluation for the adjustment or adaptation of the model was obtained through the Hosmer-Lemeshow method (8). The probability of a type I error to occur was considered that of $P < 0.05$.

RESULTS

The global UTI rate observed after the UDS was that of 3.18% (CI 95% 2.1-4.8), without distinctions between Hospitals A (2.53%), B (3.35%) or C (3.67%).

In the univariate analysis, considering the outcome of interest (presence or absence of UTI against variables such as sex, level of the injury (dichotomized as paraplegia or tetraplegia), motor injury completeness (complete or incomplete), presence of spasticity, use of antimicrobials prior to the study (Hospitals A and C), method of bladder emptying (spontaneous voiding x CIC), positivity or negativity of the basal urine culture and order of the UDS (first or second exam), no association was pointed out (Table-1).

Some of these and other variables were reviewed with regard to the existence of a possible relationship with UTI appearing after the UDS. Most of the injuries were caused by fire guns (203 cases, 30.7%), motor vehicle collisions (301 cases, 45.5%), falling from high heights (112 cases, 16.9%) and trauma over the dorsal region (40 cases, 6.1%), none of them being associated with the outcome of interest.

The patient's average age was that of 35.7 ± 11.1 years, with no distinctions between the hospitals. The patient's ages were divided in three groups for the UDS to be carried out: up to 30 years of age (237 patients, 50.1%), between 30 and 50 years of age (344, 50%) and above 50 years of age (80, 12.1%). No relationship between the patient's ages and the development of UTI was detected. The patients had been injured for an average time of 37.7 months (interquartile range 17.5 - 96.9). This average was lower amongst patients from Hospital C ($P < 0.001$). In any way, when we stratified the time since injury in up to two years, (222 patients, 33.6%), between 2.1 and 5 years (190, 28.7%) and above 5 years (249, 37.6%), we have also not found any associations with the outcome of interest.

Specifically with regard to the level of the injury, there were 116 patients (17.6%) with high cervical SCI (C1-C5), 73 (11.0%) with low cervical SCI (C6-C8), 193 (29.2%) with high thoracic SCI (T1-T6) e 279 patients (42.2%) with injuries beneath the T6 level. In no one of those four categories we observed any associations between the development of UTI and the UDS. On the other hand, dichotomizing the level of the injury between T6 or above (382 patients, 57.8%) and T7 or below (279, 42.2%), we have found that the first group presented a greater chance of developing UTI after UDS (4.5% against 1.4%, $P = 0.029$).

As for the completeness of the SCI, based on the ASIA Impairment Scale (AIS), we have classified 441 (66.7%) patients as AIS A, 82 (12.4%) as AIS B, 83 (12.5%) as AIS C and 47 (7.1%) as AIS D. In eight of the cases it was not possible to reach a classification. Once more, no relationship was found with the incidence of UTI after UDS.

After adjustments concerning the confounders from Table-1, which were carried out due to the UDS and included the patient's age and time since injury, both in years, we have not identified any independent variables. Similarly, when we tested, instead of the usage of prophylactic antibiotics, the hospital where the exam was carried out, no independent variables were identified. The only simulation that showed an association between the development of UTI and the UDS occurred when we substituted in the model the level of injuries, paraplegia or tetraplegia, by injury above

Table 1 - Categorical variables in the groups of patients with and without urinary tract infection after the UDS, with their respective odds ratios (OR; univariate analysis), confidence interval of 95% (CI 95%) and statistical significance.

Variables	Category	Urinary Tract Infection		OR	CI 95%	P value
		Yes	No			
Sex						
	Female	2	110			
	Male	19	530	1.97	0.45-8.59	0.36
Level of the injury						
	Tetraplegia	9	188			
	Paraplegia	12	452	0.56	0.23-1.34	0.19
Motor injury*						
	Complete (AIS A/B)	19	504			
	Incomplete (AIS C/D/E)	1	129	4.86	0.65-36.67	0.13
Spasticity						
	Flaccid	2	101			
	Present	17	436	1.99	0.45-8.66	0.37
Use of antimicrobials						
	No	13	363			
	Yes	8	277	0.81	0.33-1.97	0.64
Bladder emptying						
voluntary urination		5	170			
intermittent urinary catheterization		16	470	1.16	0.42-3.21	0.78
Basal urine culture						
	Negative	5	120			
	Positive	16	520	0.74	0.27-2.06	0.56
Order of the UDS						
	Second	13	371			
	First	8	269	0.85	0.35-2.08	0.72

* International Standards for Neurological and Functional Classification of SCI. (Maynard, 1997 286 /id)

or below the T6 level, which gave us an adjusted odds ratio of 3.06 (CI 95% 1.01 to 9.26; P = 0.0476). That is, independently of the usage of antimicrobials or of the hospital where the UDS was conducted, patients with a T6 level injury or above have got three times the chance of developing UTI after the exam, in relation to those with a T7 level injury or below.

DISCUSSION

This observational multicenter research trial, involving 661 patients with traumatic SCI from three units of the Sarah Network of Rehabilitation Hospitals, has not demonstrated the necessity of antimicrobials in the prevention of UTI

as a complication of UDS. The only independent variable associated with the outcome was the level of the SCI: T6 or above.

Patients with neurogenic bladder due to SCI frequently present asymptomatic bacteriuria, with no formal indication in their treatments (9). We know that this colonization can even exert a protective effect against the growth of other pathogenic agents, having proposals of inoculating low-virulence bacteria in neurogenic bladders already been made (10).

About three quarters of the studied patients used CIC as their main aid of bladder emptying and eight out of ten of those patients presented asymptomatic bacteriuria. These patients recur to CIC at least five times a day with single use catheter without the usage of prophylactic antibiotics. Both the chosen method of bladder emptying and asymptomatic bacteriuria were not independent risk factors for the development of UTI in this study, results which have already been shown by other authors (11).

The only clinical trial conducted more than two decades ago with the specific aim of answering this question has counted on just forty patients and concluded that the prophylactic antimicrobial should be indicated (5). From then on innumerable other observational research studies were carried out in order to confirm such results, since many researchers have questioned the possibility of a type I error, due to the diminished size of the sample or to the presence of potential confounders. Up to nowadays the literature is scarce with regard to the usage of prophylactic antimicrobials prior to UDS in these patients (12). The American Society of Urology recommends prophylaxis in a patient with neurogenic bladder when uroculture is positive which in fact occurs in the vast majority of cases (13).

Uncertainties involving the best conduct in the usage of antimicrobials before UDS have lead to the adoption of different conducts between the three units of the same network of rehabilitation hospitals in which we work. This situation has created the natural opportunity to compare the results obtained by each of them, with an expressive number of patients, and, with the pertinent statistical adjustments, to allow for valid conclusions, even with a retrospective observational design. All three units admit patients with traumatic SCI and neurogenic bladder, with similar clinical and neurological profiles. The only exception was the smaller amount of time since injury amongst patients from Hospital C. The three hospitals also carry the exams out by a team that was trained within the Sarah Network itself, with the same technical rigor. The main difference between the three units is the protocol for the patient's antibiotic prophylaxis before the UDS. Hospital B does not use any antimicrobials on its patients, even when they present asymptomatic bacteriuria, while the other two hospitals do use antimicrobials one to two hours before, depending on the result of the basal urine culture. Even with such peculiarities, we have not found differences on the incidence of UTI, either when we analyzed the three hospitals or when we dichotomized them into the two units that make usage of antimicrobials (Hospitals A and C) and the unit that does not use them (Hospital B).

We have found a global rate of UTI after UDS of 3.18%, which is a low rate when compared to those shown in literature, which vary between 9.7% and 15.8% (11, 12). This apparent discrepancy can derive from the fact that we do not provide medical care to patients on acute phases of the SCI, that we carry out a medical consultation prior to the exam and that we have excluded the patients with a greater risk of UTI due to the usage of a indwelling catheterization (14). On the other hand, even with such a low incidence, we had 21 infections among 661 patients, which makes it unlikely for a type II (low statistic power) error to have taken place on the differential analysis, even considering the total amount of investigated independent variables.

A provocative result found in the analysis of our data has to do with the level of the injury. Although we have not observed any associations between tetraplegia and the outcome of interest, this situation was changed when we dichotomized the level of the injury as T6 level, or as above or below the T6 level. This difference can derive from the fact that the detrusor sphincter dyssynergy and the

autonomic dysreflexia are more frequent on injuries above the thoracic sympathetic chain. In fact, we have found, both in univariate and multivariate analyses, three times more chance of occurrence of UTI after the UDS in patients with an injury that is T6 or higher, in relation to those with an injury that is T7 or lower. It is also interesting to highlight that the extent of SCI, here evaluated through the ASIA Impairment Scale, has not influenced this result, as already described on a previous study (15).

It is known that patients with tetraplegia require greater daily care, which often involves hiring caregivers, increasing the general risk of UTI, although not specifically with regard to the UDS (15). A possible explanation for the higher incidence of UTI in patients with a T6 level injury or higher could reside on a bladder ischemia that would occur in two situations: increase in the intravesical pressure (low complacency and / or high detrusor pressure) or when there is vesical hyperdistension (16). Patients with a T6 level injury or higher present detrusor sphincter dyssynergy, which enhances the resistance to urine drainage, keeping the detrusor pressure high for a longer period of time, which would diminish even more the vesical wall's perfusion. This alteration in the blood flow would retard the liberation of leukocytes and other agents of antibacterial defense interfering with the protection barriers against a bacterial invasion (translocation) and/ or bacteremia. The possibility of autonomic dysreflexia to interact with these phenomena should be considered. A study with 140 patients has shown by logistic regression a slight association between autonomic dysreflexia and UTI after UDS in patients with SCI (15). We highlight that in our univariate and multivariate analyses the use of antimicrobials has not prevented this higher chance of UTI to occur after UDS.

Like other authors, amongst the other variables of interest we have also not identified any correlation between the outcome and the patient's age (13, 14), sex (13, 14), spasticity (14), method of bladder emptying (12, 15), asymptomatic bacteriuria (12) and time since injury (14, 15).

This study presents some limitations regarding the fact that it is based on a retrospective survey of three hospital units, geographically far from each other. On the other hand, it is a multicenter study, which has allowed us to collect an expressive number of patients, so far the largest indexed on PubMed specifically on the subject. With regard to the external validity of our results, we highlight that we have considered here only patients with traumatic SCI hospitalized in rehabilitation centers. Amongst those with a non--traumatic etiology such as, for example, spina bifida, cerebral palsy, Parkinson and others, there are possibly clinical and physiopathological differences of the neurogenic bladder that might lead to a daring extrapolation of these results.

Based on a retrospective hospital cohort of patients with traumatic SCI we have demonstrated that the use of prophylactic antimicrobials would not lower the risk of UTI as a complication of UDS. The only independent variable that could be associated with that outcome was the level of the injury: T6 or above. Even in these patients the use of antimicrobials would not be justified.

CONFLICT OF INTEREST

None declared.

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Proposal of a new way to evaluate the external sphincter function prior male sling surgey

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ABSTRACT

Objective: To propose a new way to objectively evaluate the external sphincter function prior to male sling surgery.
Materials and Methods: We evaluated the pre-operative sphincter function throughout sphincter pressure at rest (SPAR) and sphincter pressure under contraction (SPUC) obtained throughout urethral profilometry profile (UPP) of 10 consecutive patients (age range, 54-79 years) treated with the retrourethral transobturator sling (RTS) for stress urinary incontinence (SUI) because of prostate surgery. The primary endpoint for surgery success rate was post-operative pad weight test. This was correlated to pre-operative pad test, RT, SPAR and SPUC. Post-operatively patients were classified as continent (no pad use) and those who still were incontinent.
Results: Mean SPUC in the continent and incontinent group was respectively 188 + 8.8 (median 185.1, range 181 to 201) and 96.9 + 49.4 (median 109.9, range 35.6 to 163.6) (P = 0.008). Mean 24-hour pad test was 151 + 84.2gm (median 140, range 80 to 245) and 973 + 337.1gm (median 1940, range 550 to 1200) in post-operative continent and incontinent groups respectively (P = 0.008). The repositioning test (RT) was positive in all continent patients except one. The RT was also positive in three incontinence patients (false positive). In all post-operative continent patients SPUC was higher than 180cmH2O and pre-operative pad test was less than 245gm.
Conclusions: SPUC seems to be a way for optimizing the sphincter evaluation as well to become a useful tool for patient selection prior to RTS surgery.

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INTRODUCTION

Retrourethral transobturator sling (RTS) is a functional, non-compressive and nonobstructive minimally invasive treatment for stress urinary incontinence (SUI). When the strict definition of continence of 0 pads / 24-hour is used, cure rates of 80% are reported as good results on selected patient cohorts (1-4). Nevertheless, a failure rate between 20% and 45% of this technique has been reported with no clearly defined reasons. Reasons for failure of the primary RTS might be related to incorrect sling placement technique, sling slippage, radiation therapy, presence of periurethral fibrosis, bladder neck contraction or incorrect patient selection (5). The key mechanism to RTS surgery seems to be a dynamic support of the urinary sphincter during stress by increasing

the coaptive zone in the sphincter part of the urethra and the ideal candidates for sling placement seem to be those with good residual urinary sphincter function (5).

Some urologists think a preoperative cystoscopy to evaluate sphincter function seems reasonable for optimal selection of patients (6). The repositioning test (RT) is a method proposed to evaluate the sphincter function on a minimally invasive way (7). A positive RT consists of contractility with a coaptive zone of ≥ 1 cm during external sphincter voluntary contraction (7). It is our belief that a possible factor influencing the outcome of the RT could be its interpretation. This is a subjective, non-numeric test, and depends largely on surgeon experience with the test. This element has not been stressed in published articles concerning repositioning slings surgeries and in particular repositioning test reports. Urethral pressure profilometry (UPP) was first described by Brown-Wickham in 1969 and was the first method used for evaluating urethral function (including sphincter pressure) (8). It is not largely used in pre-operative evaluation to male sling surgery and is more used to measure the sphincter pressure at rest (SPAR) than the sphincter pressure under contraction (SPUC) (9).

This study is a preliminary report proposing the use of the SPUC as a new and objective way to evaluate of the external sphincter function prior RTS surgery.

MATERIALS AND METHODS

Study Group

Between April 2016 and April 2017 ten consecutive patients with median age 68.5 (54-79) and duration of incontinence of 88.3 ± 71.4 months had comprehensive incontinence workup done for stress urinary incontinence (SUI). Prior the sling surgery, retropubic radical prostatectomy (RRP) was performed in 4 (40%) patients, transurethral resection of the prostate (TURP) in 4 (40%) and RRP associated with salvage radiation therapy in 2 (20%). The incontinent assessment included the International Consultation on Incontinence Questionnaire - Short Form (ICIQ--SF), 24-hour pad test, urodynamics, urethroscopy and RT. Urodynamics was performed according to the International Continence Society (ICS) recommendations (10). During urodynamics the urethral pressure profilometry (UPP) was performed to evaluate sphincter function. Measurements of SPAR and SPUC were recorded (detailed description below). RT was performed during cystoscopy to evaluate urethral mobility and sphincter function as described by Rehder P (4, 11). All patients underwent a RTS surgery and the same assessment was repeated in the postoperative (except urodynamics). Postoperatively patients were divided in two groups: continent or incontinent. Definition of continence was no pad usage.

The time elapsed between prostate and sling surgery was greater than 26 months. The surgeries were performed by two experienced urologists according to the technique described by Redher and Gozzi (12). A polyvinylidene fluoride (PVDF) sling was used, which is a highly non--reactive thermoplastic fluoropolymer produced by the polymerization of vinylidene difluoride, Dynamesh-PMR™. Exclusion criteria included the presence of anastomotic or urethral strictures on cystoscopy, high glucose blood levels (glycosylated hemoglobin higher than 7.5%), and previously failed treatments for incontinence. Informed consent was obtained from all patients and ethical institutional review board approved the study.

Sphincter pressure at rest and under contraction (SPAR and SPUC)

The SPAR and SPUC evaluation were done according to the Brown-Wickham water perfusion method of urethral profilometry profile with a 10F catheter with four holes around the circumference, 5 cm distal of the tip (8). Transducers were zeroed to atmospheric pressure at the pubic symphysis level. The catheter was introduced into the bladder. The bladder was filled with 150 mL of normal saline solution at room temperature, and with the patient in the lying position the urethral catheter was manually withdrawn. The perfusion rate was 2 mL / min. The infusion and transducer lines were connected to the bladder catheter through a three-way tap to register initial bladder pressure. The catheter was withdrawn at 1 mm /

s traction down the urethra and the pressure profile was recorded. The point of high pressure was considered the external sphincter localization. At this point the pressure was recorded as the SPAR. Then patients were asked to perform a pelvic floor contraction maneuver and the SPUC was recorded. This maneuver was repeated five times, with a three minutes interval and the medium value of the three highest SPUC were obtained for statistical analyses. Finally, the catheter was withdrawn until the holes around the circumference were clear of the external meatus (Figure-1)

Statistical analysis

The analyses of results obtained from preoperative assessment (24h-pad test, RT, SPAR and SPUC) were performed using the two-tailed Mann-Whitney U test. A P-value < 0.05 was considered statistically significant. Statistical analysis was carried out using software SAS System for Windows (Statistical Analysis System), version 9.4. SAS Institute Inc, Cary, NC, US

RESULTS

Median follow-up was 12 months (6-19). There were no major complications regarding sling implant. According to the aforementioned continence criteria the results were analyzed in two groups according to the postoperative 24h--pad test (primary endpoint). On this way 4 of 10 (40%) composed the continent group and 6 of 10 (60%) the incontinent one. The ICIQ-SF score in the preoperative in the continent and incontinent group were respectively 17.7 ± 1.2 and 18.3 ± 2.3 (p = 0.51). In the postoperative period this score in continent and incontinent groups turned respectively to zero and 14.6 ± 2.42 (p = 0.01). There was also no significant difference in preoperative urodynamic parameters between continent and incontinent groups.

The main results of this study are resume in Table-1. Pre-operatively 24-hour pad test in the continent group was 151 ± 84.2 gm (median 140, range 80 to 245) and in the incontinent group was 973 ± 337.1 gm (median 1940, range 550 to 1200) (p = 0.008). Mean SPAR in the continent and incontinent group were respectively 65.2 ± 22.5 cmH_20 (median 62.8, range 40.6 to 94.6) and 39.5 ± 12.9 (median 41.1, range 23 to 58) (p = 0.03). Mean SPUC in the continent and incontinent group were respectively 188 ± 8.8 cmH_20 (median 185.1, range 181 to 201) and 96.9 ± 49.4 cmH_20 (median 109.9, range 35.6 to 163.6) (p = 0.008). In all continent patients SPUC was higher than 180 cmH_20. The RT was positive in 3 / 4 continent patients and 3 / 6 in of the incontinence patients (false positive). The SPUC in false positive

Figure 1 - SPAR (bottom arrow) immediately before the voluntary contraction that leads to SPUC (top arrow).

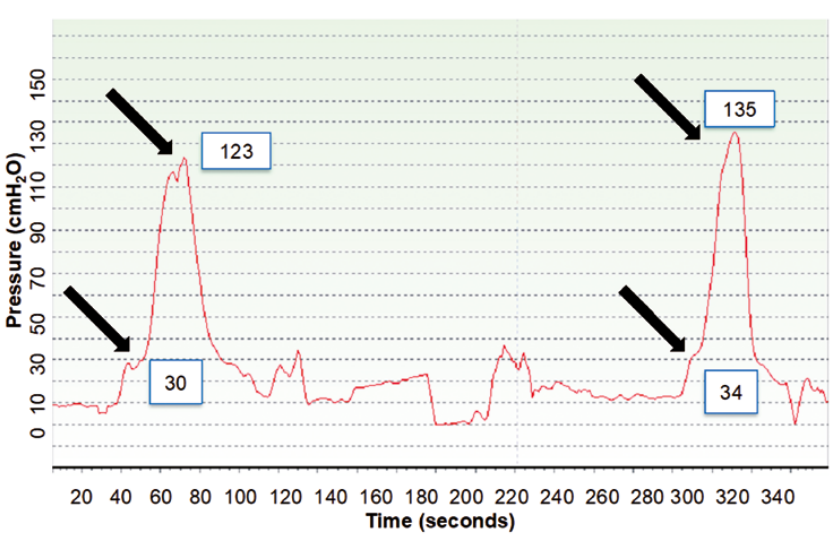

Table 1 - Pre and postoperative 24-h pad test, SPAR, SPUC and RT in postoperative continent and incontinent patients.

	24-h Pad test (gm)				
Patients	Preop	Postop	SPAR(cmH_2O)	SPUC(cmH_2O)	RT
Continent					
#1	80	0	40.6	184.3	positive
#2	200	0	67.3	181	negative
#3	80	0	58.3	186	positive
#4	245	0	94.6	201	positive
Incontinent					
#5	740	100	58	163.6	positive
#6	1200	570	27	35.6	negative
#7	750	400	23	120	positive
#8	1400	670	40.3	42.3	negative
#9	550	320	42	100.6	positive
#10	1200	600	47	119.3	negative

RT patients were 163.6, 120, and 100.6 cmH_20 respectively. RT was negative in no continent patient (false negative) and in 3 / 6 incontinent patients. All patients with low weight pad test (under 245 gm) presented with high pressure SPUC (over 180 cmH_20) and achieved complete continence. In the two patients with very low SPUC (patients #6 and #8) the repositioning test was negative and the pad test had high weight. Even in patients that did not achieve complete cures (SPUC < 180 cmH_20) there was a positive correlation between SPUC and postoperative pad test values. In the patient with the SPUC 163.6 cmH_2O the pad test reduction was better compared to patients with SPUC 120 cmH_2O or lesser (85% vs. 42-52% reduction) (Table-2).

Table 2 - SPUC and percentile of improvement.

SPUC (cmH_2O)	Pad test reduction
≥ 180	100%
163.6	86%
120	50%
119.6	46%
100.6	42%
42.3	52%
35.6	52%

DISCUSSION

This study is a preliminary report proposing the use of SPUC as an objective way to evaluate the external sphincter function prior to male sling surgery. Reasons for primary sling failure are still poorly understood and may be related to an inappropriate indication or technique (13). Patient selection is probably the most important factor related to sling surgery results but there is still not complete standardization on the selection methods used (14). An "ideal" patient to sling implant is described as a non-irradiated, with no previous urethral surgeries, only mild-to-moderate UI with a threshold of 200 gm on a 24-h pad test, cystoscopy should exclude concomitant urethral strictures / bladder neck contracture and the repositioning test should assure good urethral mobility and sphincter coaptation (15). Beside these statements papers still cannot explain why some "ideal" patients do not get completely dry and why some "no ideal" patients get dry. As demonstrated, the reported rate of RTS failure is 20% to 45.5% (13). To get these answers and consequently better results Rehder et al. presented a review explaining the potential mechanism of RTS in the therapy of post-prostatec-

tomy UI (16). These and other authors agree that the key mechanism seems to be a dynamic support of the sphincter during stress by increasing the zone of coaption in the sphincter part of the urethra (5, 16). To the authors a preoperative evaluation of sphincter function appears to be an important aspect for optimal selection of patients. Other papers also highlight the importance of preoperative endoscopic evaluation whilst only pad usage is shown to be an independent predictor of success (2, 19, 20). In a single-center prospective study Bauer et al. reported 65 consecutive patients with SUI after radical prostatectomy submitted to the repositioning test. Preoperatively patients were classified as positive and negative RT. 53 patients (81.5%) showed preoperatively a positive RT and 12 patients (18.5%) a negative RT. After a follow-up of 12 months, patients with positive RT showed a cure rate (0 pads / day) of 83% and patients with a negative RT showed only a cure rate of 25%. A positive RT significantly correlated with cure in outcome ($p < 0.001$) (7). This ideal group with SUI to be treated with repositioning slings includes patients with only mild-to-moderate urinary incontinence, no nocturnal urinary incontinence, no prior history of radiotherapy and positive RT (6).

In our opinion, RT is extremely observer dependent. The correct classification of positive or negative test is completely visual and may vary between observers. Therefore, the RT is a subjective and non-numeric test. It is also hard to compare RT results and consequently preoperative characteristics between different cohorts. This test seems to be very useful in the selection but its subjectivity may be a barrier to a widely usage. In our cohort false positive rates in RT were found in 30% of the patients, which may be a possible explanation to failure rates on "ideal" candidates to RTS. The RT was positive in three patients that did not achieve complete continence. In these three patients, SPUC were respectively 163.6, 120 and 100.6 cmH_2O demonstrating that they presented contraction but not enough to get continence after sling implantation. Nowadays pad test seems to be one of the best-studied and accepted predictors of success. Collado Serra et al. demonstrated that preoperative 24-hour pad weight correlated inversely with the outcome (odds ratio 0.996), with a 0.4% decrease in cure rate for each 1g increase in the preoperative 24-hour pad weight (21). Rehder et al. also described a 1-year postoperative success rate (defined as 1-2 pad per day and > 50% reduction in pad use) with the Advance® sling of 94% (107 of 114 patients) (22). In our study, all patients that presented with SPUC values higher than 180 cmH2O had low weight pad test (under 245 gm) demonstrating good correlation between the two methods. The big question for pad test usage only is if there are patients with higher pad test volumes and good residual sphincter function that could be included on sling protocols. One interesting paper, Malik et al. reported the variability of the pad test according to the amount of physical activity performed by the patient on the day of collection. According to the author, as higher the degree of physical activity on the day of collection the higher will be the pad test weight (23). This aspect reinforce our hypotheses that lower values in the pad test can lead to false "ideal" patients and the objective evaluation of sphincter function could help selecting patients to RTS surgery. To the best of our knowledge, there is no report using the SPAR and SPUC to predict success in RTS surgery. Commiter et al. studied the correlation among maximal urethral closure pressure, retrograde leak point pressure, and abdominal leak point pressure in men with postprostatectomy stress incontinence (9). All these pressure measurements are different from the measurements performed in this study. On this preliminary report, the SPAR and SPUC (especially SPUC) presented good association with sling surgery success.

Possible criticism to this preliminary report are the different etiologies for incontinence with a mixed cohort of post TURP and post PRR patients without details on radiotherapy and high values of pad test patients. Our arguments for mixed cohort are that our main objective was to evaluate the sphincter function independent of the etiology of incontinence. Kretschmer et al. published long-term outcome of the RTS after TURP in a cohort of 15 patients with a median follow-up of 70 months (range, 18-83 months) and mean daily pad usage was 1.8 ± 2.1 pads. Cure rate was 46.7%, and cure-and-improved rate was 60.0% (2). The authors

concluded that AdVance® and AdVanceXP® implantation can be performed effectively and safely in men suffering from SUI after TURP. However, long--term success rates seem to be lower compared to SUI after radical prostatectomy and patients should be counseled accordingly. In our cohort the separate assessment of post-TUR patients has showed that the degree of sphincter injury is more important than the etiology of incontinence when deciding whether or not to include a patient in a sling protocol. Two of our TURP patients that presented low volume of pad test and high SPUC in the preoperative period values were cured (patients #1 and #2). One of them presented SPUC of 163 cmH2O and had a reduction of 86% in the volume of losses using only 1pad / day (patient #3). The last one (patient #4) presented with a high pad test with low SPUC value evolving with great reduction of the pad test but still incontinent (Table-1). This is in line with the literature and we believe that the results of the RTS post TURP can be optimized with a better preoperative evaluation of the sphincter function. Before criticisms related to the large volumes of pad test of patients submitted to sling surgery it is important to understand that there are economic disparities on the planet we we all live. In our country more than half of the population does not have medical insurance and for the patients in this cohort the access to the AUS was completely out of possibilities. In Brazil, the final cost of an AUS is US$ 25.000.00 versus US$ 12.000.00 (also current coin relation is 3.4 R$ = 1 US$) and for these patients the sling surgery is frequently the only hope to improve the incontinence rates. In cases that the gold standard is not possible even a reduction in pad usage represents a huge impact on patients quality of life. It is also important to note that in this study even among patients with large loss volumes in preoperative pad test a reduction of 50% in almost of them was achieved. The large pad test weight in some of the subjects enrolled in this protocol was also important to better understand the sphincter function in these particular situations. Every patient with high pad test weight enrolled in this protocol was aware that the AUS was the gold standard to fix their problem but given the circumstances (impossibility to get an AUS implant due high costs) all of them fully agreed to undergo to the sling surgery even knowing that they would not be cured but glad with the perspective that they would need to buy and change fewer diapers per day.

The main limitation to our study is the small population of patients. Once this is a proposal of new way to measure the sphincter function before sling surgery we do not have comparison studies to confirm our data. More patients are just enrolled in our protocol and we hope to show more data soon. Other centers reproducing the technique and comparing to sling surgery results are welcome. Another important limitation is related to the technique employed in the measurements of SPUC. The ICS published standards on urethral pressure measurement in 2002, but internal and external consistency, retest reliability, and sensitivity to change have never been quantified (24). Also, there is no agreed-upon approach to ensure high quality (reliable and valid) urodynamic testing at maximum urethral closure pressure and during pelvic floor muscle contraction (25). In spite of these limitations, we believe that an objective sphincter pressure cut off value could be an additional tool to help both surgeons and patients to decide what surgical method to choose to fix incontinence in men.

CONCLUSIONS

This is a preliminary report proposing the use of SPUC as objective evaluation of the external sphincter function prior male sling surgery. SPUC needs to be reproduced in larger cohorts to be validated and standardized but seems to be a way for optimizing the sphincter evaluation as well to become a useful tool for patient selection to RTS surgery.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Can quadrivalent human papillomavirus prophylactic vaccine be an effective alternative for the therapeutic management of genital warts? an exploratory study

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ABSTRACT

Objective: To evaluate the treatment effect of genital warts, we investigated the quadrivalent HPV vaccine injection compared with surgical excision.
Materials and Methods: This prospective study included 26 patients (M:F = 24:2) who received HPV vaccine or surgical excision. After explanation of surgical excision or HPV vaccine, 16 patients underwent surgical excision and the others received HPV vaccine injections. Based on gross findings of genital warts, treatment outcomes were classified as complete response (no wart), partial response, and failed treatment.
Results: Among enrolled patients, 42% (11 / 26) patients had recurrent genital warts. In vaccination group, complete response rates of genital wart were 60% following 3 times HPV vaccine. Partial response patients wanted to excise the genital lesions before the 3 times injection, because they worried about sexual transmission of disease to their sexual partners. One patient underwent surgical excision after 3 times injection. Excision sites included suprapubic lesions, but other sites including mid-urethra and glans showed complete response after injection. At a mean follow-up period of 8.42 ± 3.27 months, 10 patients (100%) who received HPV vaccine did not show recurrence.
Conclusion: The response rates after HPV vaccine injection were 90% (complete and partial). Our results suggested that HPV vaccines could be effective in management of genital warts.

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INTRODUCTION

Human papillomavirus (HPV) is the source of the most common sexual transmitted disease, which could infect the mucosa and skin of the anogenital regions. Infection with HPV causes a large proportion of uterine cervix, vaginal, vulvar, anal, and penile cancers, as well as genital warts. Completion of the HPV vaccine series is important to protect adolescents against the most common HPV types associated with cervical and penile cancers as well as genital warts before they are exposed to the virus (1). High risk HPV types, such as types 16 and 18, have been known to be the most common and carcinogenic, and these 2 HPV types were responsible for about 70% of the cases of cervical cancer (2).

Therefore, the Advisory Committee on Immunization Practices recommends HPV vaccination for girls and boys aged 11 or 12 years. Routine recommendation is quadrivalent HPV vaccine for girls and boys, or bivalent vaccine for girls at

the age of 11 or 12 years (3). Quadrivalent HPV vaccine contains four HPV type-specific VLPs prepared from the L1 proteins of HPV 6, 11, 16, and 18. Bivalent HPV vaccine contains two HPV type-specific VLPs prepared from the L1 proteins of HPV 16 and 18. Both the vaccines are individually administered in a 3-dose schedule. Currently, World Health Organization recommends that adolescent girls and boys should receive 2 doses of HPV vaccine at 0 and 6 months, rather than 3 doses as reported previously, for the protection from HPV-related cancers (4). Because 2-dose schedule increases the flexibility in the interval between doses, which may facilitate vaccine uptake, HPV vaccines are recommended for girls and boys younger than 15 years of age.

Low risk HPV types, such as type 6 and 11 are the most frequent cause of genital warts (5). They are transmitted through direct skin-to-skin contact, usually during oral, genital, or anal sex with an infected partner. The treatment options for genital warts are the use of podophyllotoxin, imiquimod, or trichloracetic acid, and surgical excision (6, 7). Treatment options depend on the diagnosis, size, and location of the lesions, but local treatment could not eradicate HPV cells completely. Additionally, reduction in infectivity of HPV-related lesions by these therapeutic options is still unknown (6). With regard to the recurrence of genital warts, there is an inadequacy of controlled trials on the recurrence of warts in adults (7, 8). HPV vaccines have been known to exert protective effect on cervical cancer and genital warts, but the treatment effect is unknown. Therapeutic vaccine for HPV aims to generate cell--mediated immunity (6). Recently, some case reports showed the therapeutic effect of HPV vaccine at peri-anal and finger lesions (9, 10). We investigated the use of quadrivalent HPV vaccine injection for the effective treatment of genital warts.

MATERIALS AND METHODS

From January 2015 to December 2016, a prospective trial was conducted on 24 male patients and 2 female patients who received HPV vaccine or underwent surgical excision. Patients were evaluated for medical history, and physical examination was conducted by routine laboratory studies before vaccination. If urethral involvement was suspected, cystourethroscopy was performed.

Recurrence of HPV was also inspected by noting the history and included 14 patients who were treatment naive, while the remaining patients had received repeated freezing, laser therapy, electrocautery, and / or other treatments.

Numerous HPV lesions within clear boundary masses with mostly wide pedicle and moist smooth surface were observed. Occasional fused lesions were also present in some patients and the majority of lesions were gray-brown in color, while a few were dark red. The HPV lesions were counted carefully. All patients were confirmed to have condyloma acuminatum by pathological review.

The potent therapeutic effect and an additional preventive effect of the HPV vaccination treatment was discussed with the patients. Then, the patients decided if they should be vaccinated initially and undergo definite treatment later if there was no response after vaccination. In cases of the patients who underwent definite surgery first, we reviewed the reason by a survey.

The HPV vaccine injection group received 3 doses (Gardasil®, Merck, Kenilworth, New Jersey) within 6 months. After first injection , the second injection was done around 2 months later and the third injection was administered around 6 months after first injection.

Surgical excision of the condyloma was performed using a surgical blade. At first, masses were excised as much as possible by blade then electrocauterization was done optionally in bleeding focus.

Treatment outcomes were assessed based on the gross findings of the condyloma lesion. After vaccine injection or surgical excision, no gross condyloma lesion was classified as complete response. The cases in which more than half of the lesions disappeared by treatment, were defined as partial response. In addition, if more than half of the lesions remained or aggravated at the follow--up visit after third injections in 6 months, the patients were classified as failed treatment.

RESULTS

We conducted a prospective trial using 26 cases of HPV genital infection. Table-1 reveals the

Table 1 - Treatment outcome in 26 HPV genital infection cases. Sixteen patients underwent surgical excision and 10 were administered vaccine.

	Surgical excision (n=16)	HPV vaccine injection (n=10)	P - value
Base line characteristics			
Sex			
M/F	15/1	9/1	0.064*
Age (year)	35.8±11.2	26.1±6.0	0.016†
Condyloma recurrent history			**0.076†**
None	11 (68.75%)	4 (40%)	
More than once	5 (31.25%)	6 (60%)	
Condyloma counts			**0.242†**
1	3 (18.75%)	1 (10%)	
2-4	3 (18.75%)	5 (50%)	
≥ 5	10 (62.50%)	4 (40%)	
Treatment response			
Complete response after injection	Not assesed	6 (60%)	
Partial response after injection	Not assesed	1	
No response		3	

*: Mann-Whitney test

†: Fisher exact test

treatment outcomes in our cohort. Among the 26 patients, 16 underwent surgical excision and 10 were administered vaccine. The mean age of patients undergoing each of the treatment was 35.8 ± 11.2 years and 26.1 ± 6.0 years, respectively.

About 42% of the patients had a history of genital warts that recurred more than once. Absolute results of recurrent infection were 60% in vaccine injection patients and 31.25% in surgical excision patients. In case of the HPV lesion, only one condyloma was counted in 18.75% / 30%, two to four in 18.75% / 30%, more than five in 62.50% / 40% in surgical excision and vaccine injection patients, respectively.

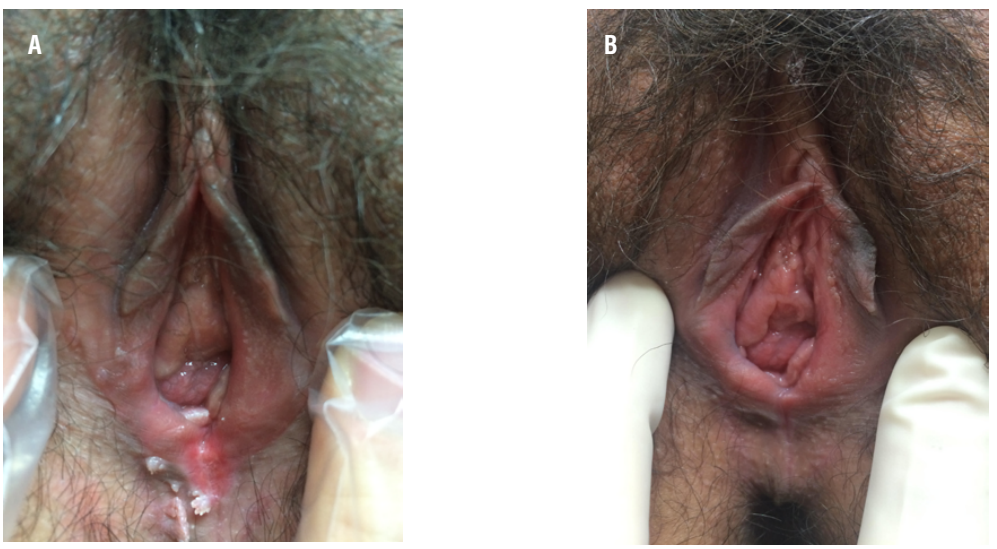
Complete response rates of genital wart were observed to be 60% following 3 HPV vaccine injections at a mean follow-up period of 8.42 ± 3.27 months. In a case of complete response by vaccination, a 36-year-old female patient had multiple HPV lesions on the external genitalia and around the urethral meatus as shown in Figure-1a, and the HPV lesions disappeared completely as shown in Figure-1b. After three vaccinations, partial response patients wanted to excise the genital lesions before the 3 injections, because they were worried about sexual transmission of the disease to their sexual partners. Three patients with no response underwent surgical excision after 3 HPV vaccine injections.

Among 16 patients who underwent surgical excision, 8 (43.75%) had expensiveness as the major concern, followed by 3 who were worried about treatment failure (18.75%), 2 worried about sexual transmission (12.5%), 2 worried about side effects (12.5%), and one patient did not answer the question.

DISCUSSION

HPV is a DNA virus from the papillomavirus group with more than 170 family types (11). HPV resides in the basal cells of the stratified squamous epithelium and squamocolumnar junction of the cervix. Therefore, systemic immunological reaction may be prohibited.

Figure 1 - (a) Multiple HPV lesions on the external genitalia of a 36-year-old female patient; and (b) the HPV lesions disappeared completely after vaccination.



Most of HPV infections are temporary and asymptomatic and raise no medical problems. Seventy percent of new HPV infections are self--limited within 1 year, and almost 90% are cleared within 2 years.

The duration of new infections is 8 months in average (12). The risk for persistence and development to precancerous lesions is designated by HPV type, with HPV 16 being more aggressive than other high-risk HPV subtypes. Issues related to cancer progression in epidemiologic data were smoking, increased age, history of sexually transmitted infections, immunologic suppression, and other host factors. The time between primary HPV infection and progress of cancer usually take decades (13).

Irrespective of the localization, HPV invades until the glandular epithelium of the cervix resulting in glandular cancers, such as carcinoma in situ or invasive adenocarcinoma (14). The HPV vaccine is intended to prevent people from getting infected with the virus, but in some cases, it may actually work as a treatment, clearing warts in people who are already infected. In the United States, about 47 million new HPV outbreaks occurred every year and caused considerable personal morbidity and social burden (15). Until now, owing to improvement in topical therapeutic approaches, surgery can be circumvented in several cases (16). Nonetheless, surgical intervention is the representative treatment in most of the cases, especially, in high risk condyloma or if regional therapy does not seem viable owing to the unfavorable size or location of the affected site.

The natural history of naturally acquired immunity related to HPV is poorly understood. HPV vaccine has been valid for routine vaccination of juvenile girls since 2006. It is true that HPV vaccination has been mainly focused on young female patients. Irrespectively, HPV vaccine has been proven to also be useful in male patients for the prevention of HPV recurrence and its associated malignancies. Recently, HPV vaccine has been permitted to be used for male patients in several countries as well (17, 18). The Brazilian Ministry of Health does not recommend that as a public health guideline, but the Brazilian Agency of Sanitary Surveillance (ANVISA) indicates that vaccination in women aged 11 to 26 years (19).

Consequently, HPV vaccine has been shown to be potent in preventing genital warts and related cancers in both genders. Vaccine is a medical agent that generates antibody and provokes a subclinical immunological effect in the human body by enhancing immunity to the specific infection. HPV creates warts in various proportions of

the cervix, vagina, and vulva in female patients; the penile and scrotum areas in male patients; as well as the anal area in both genders. Therefore, completion of the HPV vaccination series is essential to protect patients against the most common HPV types associated with genital warts previous to the exposure of HPV.

Recently, the idea of vaccination was extended to the concept of its therapeutic usage. Sustained expression of the HPV oncoproteins, E6 and E7 are crucial factors in the development of intraepithelial neoplasia and cancers, and thus, creating main targets for therapeutic vaccines (20).

In the cervical HPV infection, complete response of cutaneous warts was noted after 3 injections of the vaccine (21). Another patient with exophytic wart masses on the perianal area had dramatic regression after a single course of HPV vaccination (9). However, most clinical trials of vaccines against HPV-related diseases have focused on pre-cancers and cancers of the cervico--vaginal area.

Even though HPV vaccine was intended to produce neutralizing antibodies to avoid reinfection, its abilities to induce cell-mediated immunological responses were confirmed in previous studies (22, 23). Additionally, adoptive T cell transfer therapy has been recently evaluated in patients with metastatic cervical cancer, and the proportion of clinical response with HPV-specific T cells was 33%; the case reports providing significant evidence that HPV-related disease can be susceptible to T cell-mediated mechanisms are limited (24). Therefore, the rapid therapeutic reaction of HPV vaccination had relevance in the activation of the immunological system, including T cells and macrophages.

Some previous clinical trials assessing the outcomes of therapeutic HPV vaccinations showed unsatisfactory results, and studies on therapeutic vaccines against HPV are mainly being published as case reports as discussed above (25). On the contrary, experimental trials with positive effect were also conducted. Fifty-four female patients with high grade cervical intraepithelial neoplasia (CIN) were administered MVA E2 (vaccinia virus Ankara containing the bovine papilloma virus E2 protein) therapeutic vaccine. Total elimination of high-grade lesions was observed in 20 out of 34 patients with MVA E2 vaccine. Eleven patients showed reduction in size by more than half and in three other patients, the warts were decreased to CIN 1 or 2 (26).

Recent experimental study on the combined use of the imiquimod 5% cream and quadrivalent recombinant HPV vaccination to achieve long-term clinical remission of chronic HPV infection manifested by anogenital warts was published. This study enrolled 36 young patients (22 men) that were vaccinated by quadrivalent recombinant and co-administered with imiquimod 5% cream three times in a week up to four months. Complete remission of genital warts was observed in 94.4% patients within 1 year and 2 patients with anogenital warts were treated with Solcoderm® cream which completed the removal of genital warts. There were no recurrences throughout follow-up period (27).

Another report showed noninferiority of the immune reaction in males (age 10-15 years) compared with same aged female group, and in males (age 9-15 years) compared with same females group it was demonstrated that both geometric mean titer and seroconversion rates for all four HPV vaccine types met non-inferiority criteria in the per-protocol population. So we may expect the similar treatment effect irrespective of gender (28).

Our case series is the first to reveal the therapeutic effect of HPV vaccination. The response rates of 90% (complete and partial) after vaccine injection were promising. Besides, our idea of therapeutic vaccination on the genital warts is based on some valuable merits. Firstly, genital warts are not a fatal disease, so we can choose a treatment from multiple options considering various factors, and definite surgical treatment could be deferred after systemic vaccinations. Additionally, therapeutic vaccination is relatively non-invasive, because surgical management may induce pain and scar formation. Furthermore, we should be cautious about viral seeding during ablation procedure. If HPV infects the cervix, approximately 90% of the infections are cleared without any management within 2-3 years even though variation de-

pends on their type and risk of HPV. Cellular immunity plays an important role in this natural loss of HPV infection (29, 30). This means that immunological aspect is crucial for therapeutic clearance of HPV infections, with vaccination occupying important part in preventive advantages. Lastly, HPV does not invade the epithelium and systemic defensive reaction by antibody cannot be induced. Thus, major preventive advantage by therapeutic vaccination is definitive compared with that by curative local management (12). Though our successful data on complete response on vaccination treatment could be merely reflection on the tendency toward faster resolution of HPV infections, no one can conclude that therapeutic vaccinations are valuable medical therapy or just secondary assistant management with minimal merits.

HPV vaccines as a treatment option have to overcome several hurdles. Therapeutic vaccination has not been officially evaluated in a randomized prospective trial and accordingly it has not received a formal approval in any country. Therefore, there remains a critical necessity for clinical trials to evaluate the efficacy of HPV vaccination as a treatment. We need to understand the difference in clinical response of patients after vaccination for treatment of HPV infection. Various concerns of patients who underwent curative resection, such as expensive cost, treatment failure, sexual transmission, should be overcome by cost analysis or education about the barriers during the treatment period.

Some patients who were administered with HPV vaccine for the management of genital warts, were worried about sexual transmission to their partners. They underwent surgical excision during the vaccine administration period and the infection did not recur during the follow-up. So, to maximize the efficiency of the vaccine, the possible candidates should be vaccinated irrespective of the gender and condition of the patients.

This research has several limitations, such as small number of patient group and no prospective randomized control group. Additionally, we do not have HPV typing result and biomarkers for immunological responses or risk level. We explained potent therapeutic effect of vaccine that was not fully proven for genital warts. So this may introduce a very strong bias and misinformation in the consent process. Patients were mixed with the first episode and recurrent episode, so the immunology issues may be different in both cases. Furthermore, we do not know the optimal dose or regimen enough to protect and we should not know the age-related treatment option even many countries are not limiting the age for people to get the prophylactic vaccine.

Even though our study has some drawbacks, our data on therapeutic vaccination shows its potential benefit as an excellent treatment candidate to motivate clinical regression in genital warts.

Genital warts remain a serious issue worldwide because early diagnosis is difficult and proper primary management is sometimes missing. In the absence of vaccine coverage, the presence of high number of HPV infections, and the incidence of HPV-related tumors will remain a global public concern worldwide, including Korea. In conclusion, classical concept of vaccination is to generate beneficial immunological effect in the body to prevent recurrences. In our opinion, therapeutic HPV vaccination can eliminate genital warts, leaving people with better protection against future recurrences caused by HPV relapse.

CONCLUSIONS

The response rates of our research after therapeutic HPV vaccination indicated effectiveness as an initial management approach of genital warts with potent preventive advantages over recurrent infection.

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CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Hematologic parameters and Neutrophil / Lymphocyte ratio in the prediction of urethroplasty success

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ABSTRACT

Objective: The pathophysiology of urethral stricture and its recurrence remains vague and one of the important causes is progressive inflammation. It has been shown in recent years that the neutrophil / lymphocyte ratio is a marker of systemic inflammation and is associated with prognosis in many cardiovascular diseases, malignancies and chronic inflammatory diseases. We assessed simple systemic inflammation markers preoperatively and surgical techniques for urethral stricture recurrence after urethroplasty.

Patients and Methods: After exclusion criteria applied, a total of 117 male cases operated with urethroplasty in our clinic between January 2012 and June 2017 were included in the study and analyzed retrospectively. Localization and length of the strictures of the patients, neutrophil counts and percentages, lymphocyte counts and percentages, and neutrophil / lymphocyte ratios in preoperative peripheral blood samples were statistically analyzed. Recurrent stricture during first 12 months follow-up after the surgery has been assessed as recurrence.

Results: The mean age of the patients was 54.12 ± 16.35 and the mean urethral stricture length was 3.44 ± 1.83 cm. Recurrence was observed in 30.1% of cases who received buccal graft, 30% in penile skin applied cases and 26.1% of cases treated with end-to-end anastomosis and there was no statistically significant difference between neutrophil, lymphocyte, neutrophil / lymphocyte ratio and average stricture segment length between recurrent and non-recurrent cases ($p > 0.005$).

Conclusions: We consider that neutrophil, lymphocyte counts and their ratio prior to urethroplasty and the technique performed are not parameters that can be used to predict stricture recurrence. Prospective and randomized new trials with larger patient populations are needed to make more accurate judgments about the role of these inflammatory parameters.

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INTRODUCTION

Urethral stricture is a pathology caused by fibrosis and stenosis of the urethral epithelium and corpus spongiousum, leading to lower urinary tract symptoms and therefore, it is a troublesome problem in urology for both the patient and the physician. It can significantly disrupt quality of life and can cause serious amounts of health expenditure. At present, the incidence of urethral stricture may be iatrogenic due to increased application of transurethral procedures in urology

practice, as well as trauma, urethral catheterization, and urinary infections (1).

The treatment of the urethral stricture varies according to the location, length, and type of stenosis, and endoscopic methods are generally preferred because they are simpler, more economical, and repeatable (2). According to the guidelines, urethroplasty is recommended when the segment of the stenosis is 2 cm or more, endoscopic methods have failed, there is excessive periurethral fibrous tissue density, or a high risk of recurrence (3). The natural course of the urethral stricture is blurred, but the well-known feature is its repetitive character. For this reason, efforts to investigate different markers and treatment alternatives in order to predict and prevent recurrence are on the rise.

The neutrophil / lymphocyte ratio (NLR) can be used as a potential predictive marker to detect inflammation, which is easily calculated through blood count analysis (4). The NLR may help foresee recurrence risks after urethroplasty because inflammation is thought to have a major role in the pathogenesis of urethral stricture.

According to the literature, there are inconsistencies about the predisposing factors regarding recurrent strictures after urethroplasty, and this issue is not clear (5). To our knowledge, no other study has used systemic inflammation markers to predict recurrence after urethroplasty procedures performed due to urethral stricture. In this study, we evaluated preoperative inflammation markers in relation to the recurrence of urethral stricture after urethroplasty and surgical techniques.

MATERIALS AND METHODS

A total of 117 male patients who underwent urethroplasty due to urethral stricture in our clinic between January 2012 and January 2017 were retrospectively reviewed from the hospital electronic database after receiving written informed consent from the patients. Approval was obtained from the local ethics committee (No: 2017 / 87-15). All patients had undergone urethroplasty due to urethral stricture greater than 2 cm in various locations of the urethra. Patients with malignancies; diabetes mellitus; cardiac, pulmonary, hematologic, liver or kidney dysfunction; patients who received blood transfusions; patients with a body mass index (BMI) over 35 kg / m^2; and those with a history of previous open urethral surgery were excluded. The location and length of the stricture were calculated using retrograde urethrography and cystoscopy. Urine culture tests were performed on each patient preoperatively and the surgeries of patients with active infections were postponed until the treatment was completed. Neutrophil and lymphocyte counts were analyzed the day before the operation and the NLR was calculated by dividing the number of neutrophils by the number of lymphocytes. Blood counts of all patients were made on a stationary device in the hospital's central laboratory that is regularly checked. The location and length of the stricture, neutrophil numbers and percentages, lymphocyte counts and percentages, and NLRs in preoperative peripheral blood samples were examined in detail and statistically analyzed. All procedures were performed by a single experienced surgeon. After receiving an appropriate prophylactic single dose of antibiotic, all operations were performed in lithotomy position. In all patients it was inserted a 16-F or 18-F silicone catheter after the operation. When needed, paracetamol (1000 mg) which has less peripheral and anti-inflammatory effects, was administered intravenously once a day in postoperative period. The success of urethroplasty was evaluated through urine flow rate (maximum flow rate > 10 mL / sec) or no recurrent stricture in retrograde urethrography within 12 months after surgery.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences for Windows version 18.0 (SPSS, Chicago, IL, USA). Expression ratios were transformed into fold changes and reported as relative expression. The normal distribution of the parameters was evaluated using the Shapiro-Wilks test. Descriptive statistical methods (mean, standard deviation, frequency) were used, and Student's t-test was used to compare quantitative parameters between two

groups that were distributed normally. The Chi-square test was used for the comparison of qualitative data. $P < 0.05$ was regarded as significant.

RESULTS

The mean age of 117 male patients included in our study was 54.12 ± 16.35 (range, 14 to 84) years, and the mean urethral stricture length was found as 3.44 ± 1.83 cm. Totally, 68 patients had only bulbar urethral stricture. Other urethral stricture locations and percentages are detailed in Table-1. Most patients presented with obstructive symptoms (79.2%), while acute urine retention and suprapubic catheter fixation were the presenting symptoms in 8.7%.

Regarding the techniques used among open urethroplasty operations, the buccal graft method was used in 62.4% of cases, end-to-end anastomosis in 19.7%, penile skin flap method in 17.1%, and the bulbar method was used in 0.9% (Table-1). The mean operative duration was 132.5 ± 16.35 minutes. The mean withdrawal time of the urethral catheter was 15 (range, 12 to 21) days. A total of 34 patients (29%) had recurrence. There were no statistically significant differences between the recurrence rates according to the urethroplasty method used ($p > 0.05$). Recurrence was seen in 30.1% of cases where the buccal substitution method was used, 30% of cases with penile skin, and 26.1% of cases with end-to-end anastomosis. These results are shown in Table-2.

Table 1 - Stricture location and surgical method parameters.

	n	%
Location		
Bulbar and membranous urethra	3	2.6
Bulbar urethra	68	58.1
Distal bulbar urethra	8	6.8
Distal and proximal bulbar urethra	1	0.9
Fossa navicularis	3	2.6
Fossa navicularis and bulbar urethra	2	1.7
Fossa navicularis and penile urethra	1	0.9
Membranous urethra	2	1.7
Distal and proximal penile urethra	1	0.9
Penile urethra	15	12.8
Penile urethra and distal bulbar urethra	4	3.4
Proximal bulbar urethra	8	6.8
Proximal penile urethra	1	0.9
Method		
Buccal Graft	73	62.4
Bulbar	1	0.9
Penile skin Flap	20	17.1
End-To-End Anastomosis	23	19.7

Table 2 - Recurrence evaluation according to surgical method and blood parameters.

	Recurrence		
Method	**Yes**	**No**	**p***
	n (%)	**n (%)**	
Buccal graft	22 (30.1)	52 (69.9)	
Penile skin flap	6 (30.0)	14 (70.0)	0.931
End-To-End anastomosis	**6 (26.1)**	**17 (73.9)**	
	Recurrence		
	Yes	**No**	**p****
	Mean±SD	**Mean±SD*****	
Neutrophil	4.9±1.66	4.98±1.81	0.824
Lymphocyte	2.31±0.87	2.23±0.91	0.649
Neutrophil/Lymphocyte	2.36±1.06	2.58±1.49	0.418
Stricture length (cm)	3.41±1.76	3.46±1.97	0.907

* p value of Chi-square test
**p value of Student- t test
***Standard deviation

There were no statistically significant differences between neutrophils, lymphocytes, NLRs, and mean stricture lengths between recurrent and non-recurrent cases ($p > 0.005$) (Table-2).

DISCUSSION

Although urethral stricture has been a well--known disease for many years, urologists still strive to find a way to prevent recurrence or a curative method. Often seen in males, urethral stricture has an incidence of 0.2-1.2%, which increases over the age of 55 years (6). Anatomically, the urethra is divided into two parts: anterior and posterior. The anterior part, wrapped by corpus spongiosum, comprises two parts: penile and bulbar. The bulbar urethra lies between the penoscrotal junction and the membranous urethra. The posterior urethra is located between the bladder neck and the bulbar urethra and it comprises the prostatic urethra and the membranous urethra covered with the external urethral sphincter (7).

Penile urethral strictures can often be due to urinary intervention, urethral infection or inflammation, or can occur in older men due to ischemia. Bulbar urethral strictures are the most common site of urethral stricture, and most of these strictures are congenital or idiopathic (8). When urethral strictures are considered, fibroblasts are probably responsible for the development of the urethral stricture; however, the reason for the urethral stricture is related to the urinary extravasation into the subepithelial space causing increased inflammation and subsequent scar formation. With this knowledge, many authors have used colchicine, mitomycin-C, triamcinolone, corticosteroids, and anti-inflammatory drugs locally or systemically to reduce urethral stricture after urethral procedures (9). In this context, urethral stricture is a result of inflammatory changes in the epithelium of the urethra and can be treated by interfering with the inflammatory process. We used anti-inflammatory drugs (COX-2 inhibitors) three days after the operation to reduce inflammation in our cases.

The treatment choice after urethral stricture is related to the stricture length, location, and

recurrence. In most urethral strictures, direct visual internal urethrotomy (DVIU) or urethral dilatation is preferred as a starting treatment. In recurrent urethral strictures, DVIU is thought to cause extra scar formation, and thus the length and severity of stenosis are affected negatively. For this reason, open urethroplasty in patients with recurrent urethral strictures, long urethral stricture, or dense periurethral fibrous tissue has a higher success rate and less chance of recurrence than DVIU. The gold standard treatment for short and apparent strictures of the bulbar urethra, whether or not the lumen is completely obliterated, is excision, spatulation of both ends, and end-to-end anastomosis (10). For bulbar urethral strictures equal or longer than 2 cm, the gold standard method is stricturotomy and dorsal patch substitution urethroplasty with a buccal mucosal graft (11). Urethroplasty using carefully-prepared penile shaft skin with a rich dartos pedicle can be performed in patients with a long bulbar or penile stricture completely obstructed with extreme spongiofibrosis, even if it is not a gold standard method (12). We chose to perform open urethroplasty instead of internal urethrotomy in strictures over 2 cm and with dense fibrosis.

The reason for recurrent urethral strictures after urethroplasty remains unknown. However, it is known that there may be a relationship between past urinary procedures, patient age, mucosal damage, inflammation, and systemic diseases with urethral stricture (13). In addition, according to the literature, stricture recurrence risk is likely to increase as the length of the urethral stricture segment increases (14). This is due to the increased surface area required for a successful graft placement as the stricture length increases. This leads to ischemic strictures being seen often (15). There was no significant relationship between urethral stricture segment and urethral stricture recurrence in our study. We think that this is caused by the fact that our study did not include a wide range of groups in terms of urethral stricture length. In addition, despite evaluating factors that might cause urethral strictures in our study, no significant relationship between the development of urethral strictures after urethroplasty and preoperative neutrophil count, lymphocyte count, NLR, stricture location / length, and surgical technique was found.

In recent years, it has been shown that the NLR may be a marker of chronic systemic inflammation and is associated with prognosis in many cardiovascular diseases, malignancies, and chronic inflammatory diseases. These markers were previously assessed in various uro-oncologic cases and have been shown to have an effective role in both predicting postoperative surgical margin status and progression-free survival (16, 17). It is known that white blood cells differ in systemic inflammation, such as neutrophilia and lymphopenia (18). This inflammatory response and tissue necrosis leads to fibrosis and poor recipient vascularity, which likely has a key role in deficient wound healing, which threatens urethroplasty success (19). In a study that regarded an NLR of 2.7 as a limit, it was shown that a combination of tumor stage and NLR could be used to assess the risk of recurrence in patients with non-metastatic renal cell carcinoma (20). Another study showed that the NLR in non-clear-cell kidney tumors was an independent prognostic factor for disease-free survival after curative surgery. As such, the NLR has been reported to be a significant marker for patient counseling and clinical trial design (21). In a related study of 208 patients with a history of urethral stricture after transurethral resection of the prostate from our country, it was shown that the NLR was relatively higher in relapsed patients but not significant (9). In our study, there were no statistically significant differences between neutrophils, lymphocytes, NLR, and patients with and without stricture recurrence after urethroplasty.

A correlation between coronary artery disease, diabetes mellitus, morbid obesity, peripheral vascular disease, and chronic obstructive pulmonary disease and urethroplasty failure has been shown in previous studies (22, 23). Here, pathophysiologic components such as decreased tissue vascularity, chronic inflammation, impaired collagen synthesis, and ischemic strictures increase urethroplasty failure.

It is conceivable that there may be a correlation between increased age and recurrence of stenosis because the comorbid diseases known to be closely related to urethroplasty failure / urethral

stricture recurrence are more frequent in older patients. However, when the literature is examined, no correlation has been reported between age and urethroplasty failure (24). In our study, patients with systemic diseases that could adversely affect wound healing were excluded from the study, so the average age was not high.

The main limitations of our study are that it is single-centered, it has a relatively limited number of patients, its retrospective nature, and the exclusion of older patients due to additional comorbidities. Therefore, patients with these comorbid factors and patients with a body mass index above 35 kg / m^2 were not included in our study.

CONCLUSIONS

Neutrophil and lymphocyte count and the NLR are inexpensive, easily accessible laboratory tests that can be calculated with a simple blood count. Although it is not yet possible to say that the consideration to the surgical technique to be applied along with neutrophil, lymphocyte numbers and the NLR before urethroplasty was successful in predicting the recurrence of stenosis, we think that the presence of a systemic inflammatory response may be an important marker, as it is in oncologic cases. We believe that these laboratory findings should be supported by large series, prospective, comparative, randomized, and multi-centered studies with long-term results to detect the association of urethral stricture recurrence after urethroplasty, and to obtain stronger judgments.

CONFLICT OF INTEREST

None declared.

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Smartphone-based stent tracking application for prevention of forgotten ureteral double-J stents: a prospective study

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ABSTRACT

Purpose: Retained or forgotten ureteral stents (FUS) have a potential to cause significant morbidity as well as medico-legal issues and increased cost. We aimed to evaluate the efficacy and usefulness of smartphone-based Ureteral Stent Tracker (UST) application and compare the results with basic appointment card system to prevent FUS, prospectively.

Materials and Methods: A total of 90 patients who underwent ureteroscopic stone treatment procedure with indwelling DJ stents were equally distributed into two groups. In group-1, patients were followed using UST application. In group-2, only appointment cards were given to the patients. Two groups were compared in terms of stent overdue times and complete lost to follow up rates.

Results: Forty-four patients in group-1 and 43 patients in group-2 completed the study. Among patients, 22.7% in group-1 and 27.9% in group-2 did not return for the stent removal on the scheduled day. In group-1, these patients were identified using the UST and called for the stent removal on the same day. After 6 weeks of maximal waiting period, mean overdue times in group-1 and group-2 were 3.5 days and 20 days, respectively (p = 0.001) . In group-2, 3 patients (6.9%) were lost to follow up, while in group-1, it was none (p = 0.001).

Conclusions: We found that the patients who were followed by the smartphone-based UST application has less overdue times and lost to follow up cases compared to the basic appointment card system. The UST application easily follows patients with indwelling ureteral stents and can identify patients when overdue.

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INTRODUCTION

Ureteral double-J (DJ) stent placement is one the most common procedures in daily urological practice. The DJ stent placement is indicated in the treatment of urolithiasis, to relieve benign or malign obstruction, to promote ureteral healing and manage urinary leak (1). Most DJ stents are inserted for temporary purposes and need to be removed on maximal safe life depending on their production material. However, approximately 12% of all ureteral DJ stents are retained or forgotten (2). These forgotten ureteral stents (FUS) may lead to infection, migration, encrustation and fragmentation (3, 4). El-Faqih et al. reported that encrustation occurred in 9.2% of the stents under

6 weeks, 47.5% between 6-12 weeks and 76.3% after 12 weeks in removed DJ stents which were placed for urolithiasis (5). Furthermore, more serious complications such as sepsis, renal failure or even mortality have been reported with FUS (6). Besides the additional cost and medico-legal problems, management and removal of encrusted and infected FUS may require combined endourologic procedures and may represent a challenge for urologists (7). The attending surgeon is responsible for both monitoring the patient and safe removal of the stent. Therefore, tracking of patients with indwelling DJ stents and stent removal on a planned time is quite important to avoid increased morbidity and healthcare costs.

In order to prevent FUS, different stent tracking and registry systems have been developed including paper card registry (8), electronic patient registry (2, 4) and computer based e-mail (9) or short-message-service (SMS) reminders (10). However, these systems presented a solution only for a single institute. They required infrastructure with extra cost and secretarial entry to the system.

Today, smartphones are an integral part of our daily lives. For tracking patients with indwelling DJ stents, a cloud based smartphone application, Ureteral Stent Tracker™ (UST) was developed (11). In a prospective study, we aimed to evaluate the efficacy and usefulness of UST application and compare the results with basic appoinment card system to prevent FUS.

MATERIALS AND METHODS

After obtaining the approval of institutional ethics committee, a prospective non-randomized study was created. Patients between the age of 18 and 80 who underwent ureteroscopic laser lithotripsy for urinary stone disease and followed by DJ stent placement in our clinic were included the study. Ureteral DJ stent indications other than ureteroscopic stone surgery, patients with long--term or metallic stents for malignancy and patients with language problems were excluded to create a more homogenous patient group. Between April 2018 and July 2018, 90 of 104 patients were found eligible. In all patients, 4.8 French (F), 24-28 cm Percuflex (Boston Scientific, Marlborough, MA, USA) DJ stent was used. The indwelling time for stents was described as 2 weeks. Bilateral ureteral DJ stents were counted as 1-stent care plan if inserted simultanesously. Patients received only non-steroidal analgesics on-demand.

Patients were equally distributed into two groups consecutively based on their date of operation. In group 1, 45 patients with indwelling DJ stents were recorded to the UST application running on an iPhone 6S smartphone (Apple Inc., Cupertino, CA, USA) in addition to the appointment card for stent removal. Every day, the UST visual dashboard was reviewed by the follower to check patients with indwelling stents. In this group, patients who did not return for stent removal on the scheduled date were contacted by phone and their appointments were reminded by the follower. Patients who were unreachable were called again, once a day for 2 days. In group 2, only an appointment card was given to the patients and they were asked to return to the hospital on a scheduled date for stent removal. In both groups, patients were also verbally informed about the indwelling stent. Since there is no stent registry, this is the standart procedure in our institution. Patients in group 2 were not called to remind their appointments for stent removal. For ethical reasons, the maximal waiting period for the patients who did not return to the hospital for stent removal was limited to 6 weeks. The patients were contacted by phone in a protocol described above and invited to the hospital for stent removal if they exceeded the 6 weeks maximal waiting period. Two groups were compared in terms of stent overdue times and lost to follow-up rates.

UST* was developed by Visible Health Inc. (Austin, TX, USA) in partnership with Boston Scientific and can be downloaded from Apple Store or Google Play. However, its use is limited to physicians who are registered and pre-authorized by Boston Scientific. The UST is a password-protected, encripted, cloud-based and HIPAA compliant application for smartphones which a web browser interface also exists. The administator and privacy officer of Visible Health team have access to patient data for maintenance and support. After registering a patient with name and

medical record number, and scanning the stent product barcode, the responsible physician can create a care plan and schedule a stent extraction date (Figure-1). Creating a new case is at the POC and real-time. The application allows users to review overdue, incomplete, and indwelling lists within 2 weeks, and extracts stent patient groups (Figure-2). Once a default follower is set up, additional followers can be added to the care plan by the primary follower. Each created profile shows patient information including e-mail address and phone number, stent insertion date, laterality, scheduled stent removal date, and extraction date if the stent was already removed. It is also possible to send an e-mail reminder and attach patient information guide about the DJ stent to patients (only in English yet) if the administrator turns on this hidden feature. After the set up, UST sends daily or weekly reminder e-mails to the follower showing the list of patient groups described above.

Figure 1 - A view of ureteral stent care plan of patient (Images© Copyright Visible Health, Inc. Created for demonstration).

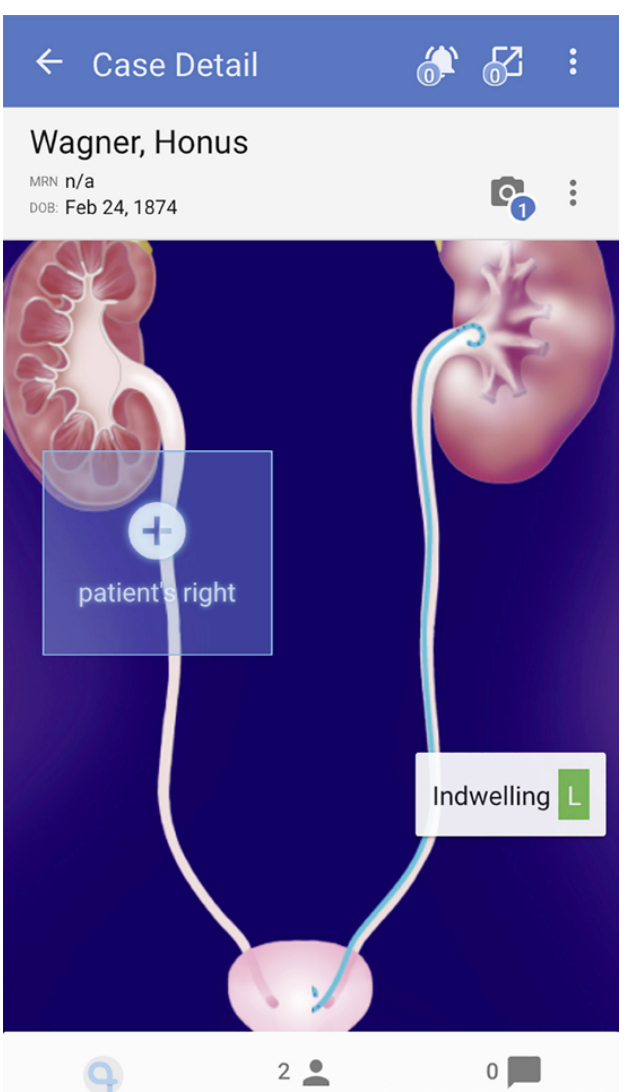
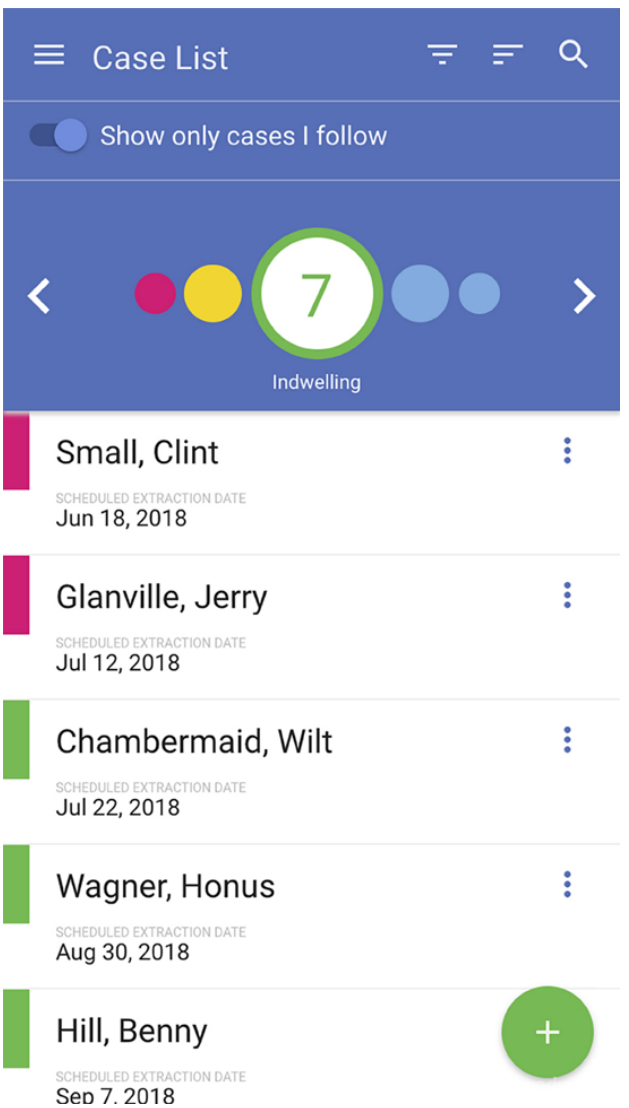


Figure 2 - A view of the UST dashboard showing overdue, incomplete, indwelling, within 2 weeks and extracted cases (Images© Copyright Visible Health, Inc. Created for demonstration).



The statistics were presented as mean ± standard deviation (SD). Distribution of variables was assessed with the Kolmogorov-Smirnov test. The Student's t test and Mann-Whitney u test were used to compare independent quantitative data. Chi-square test was used to compare qualitative data. The power of the study was calculated using the G* Power program (University of Dusseldorf, Dusseldorf, Germany), an effect size convention of 0.8 for the two-tailed t-test with an alpha error protection of 0.05. Statistical significance was assessed with two-tailed tests, and p was considered to be statistically significant when < 0.05. Statistical tests were performed using SPSS 22.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Eighty-seven of 90 patients with 87 ureteral stent care plans (44 patients in group 1 and 43 patients in group 2) completed the study. The patient's demographics are shown in Table-1. There were bilateral DJ stents in 2 patients in group 1, and none in group 2. One patient in group 1 and two patients in group 2 were exluded because their stents were removed before the scheduled date due to severe discomfort.

There was no statistical difference between two groups in terms of age, sex, educational level and laterality (Table-2). In group 1, which was tracked with the UST application, 10 / 44 (22.7%) patients missed their appointments for stent removal and returned with a mean 2.5 ± 0.9 days after a phone call by the follower. The reasons for the delay in this group were social issues in 3, and health problems in 7 cases. Similarly, in group 2, 12 / 43 (27.9%) patients missed their appoinments. On the other hand, 9 of 12 patients who missed their appointments in group 2 returned for stent removal within 6 weeks period with a mean 16.3 ± 5.0 days overdue.

The delay reasons of these 9 patients were social issues in 7 and health problems in 2.The remaining 3 patients (6.9%) were considered as lost to follow-up and contacted by phone and invited for stent removal since they had exceeded 6-week-maximal-waiting-period for the study. In these 3 cases, forgetting the existence of the stent was the main reason for failing to return for stent removal. All stents were removed in both groups. Among patients who did not return for stent removal, statistical evaluation revealed that patients in group 1 had significantly less overdue times (p = 0.001) and lost to follow-up cases (p = 0.001) compared to group 2.

DISCUSSION

With developments in endourology and minimal invasive procedures, the numbers of indwelling DJ stents have increased. The high volume of ureteral DJ stents increase the number of retained or FUS. The reasons of FUS are not clear. Divakaruni et al. have tried to identify the risk factors for FUS (2). They concluded that males were 2.5 times more likely to have FUS than

Table 1 - Patients' demographics.

		Min-Max	Median	Mean±s.d/n-%		
Age		20.0-80.0	48.0	48.6	±	14.5
Sex	Male			54		62.0%
	Female			33		38.0%
Education level	Primary			27		31.0%
	High			36		41.4%
	University			24		27.6%
Stent side	Left			43		49.4%
	Right			42		48.2%
	Bilateral			2		2.4%

Table 2 - Results and comparison of the two groups.

		Group 1				Group 2				*p*	
		Mean±s.d/n-%			Median	Mean±s.d/n-%			Median		
Age		50.0	±	15.0	48.5	47.2	±	14.0	46.0	0.430	t
Sex	Male	25		73.5%		19		57.6%		0.169	X^2
	Female	9		26.5%		14		42.4%			
Education level	Primary	9		26.5%		10		30.3%		0.439	X^2
	High	15		44.1%		14		42.4%			
	University	10		29.4%		9		27.3%			
Side	Left	17		50.0%		16		48.5%		0.901	X^2
	Right	17		50.0%		17		51.5%			
Overdue* (day)		2.5	±	0.9	1.9	16.3	±	5.0	12.2	0.001	m

^{t} = t test; ^{m} = Mann-whitney u test; $^{X^2}$ = Chi-square test; * = patients not returning for stent removal

females, and patients without insurance were nearly 6 times more likely to have FUS compared to insured patients. Employment status, educational level, and ability to speak English were not in association with FUS in this study.

Despite progress in stent and biomaterial technology, FUS is still associated with significant morbidity. The most commonly used DJ stents are polyurethane and have an average indwelling time ranging from 3 to 6 months. It is clear that there is a correlation between the ureteral stent indwelling time and biofilm formation and encrustation (5, 12). Kawahara et al. investigated stent encrustation and morbidity related to indwelling time (3). In a total of 330 stents, they found that the encrustation rate was 26.8% in less than 6 weeks, 56.9% in 6 to 12 weeks, and 75.9% in more than 12 weeks. Monga et al. reported a series of FUS left in situ for a mean of 22.7 months, and 68% were calcified, 45% were fragmented, and 14% were calcified and fragmented, respectively (7). These infected and encrusted FUS may lead to complications ranging from simple urinary system infection to septic shock and even death (6). The negative effect on glomerular filtration rate (13) and renal failure has also been reported with FUS (14). Furthermore, management of infected and encrusted FUS can be a challenge, especially in solitary kidneys. Removal of a highly encrusted FUS may require extracorporeal shockwave lithotripsy (ESWL) or endourologic procedures including cyctolithopaxy, ureterorenoscopy (URS) and percutaneous nephrolithotomy (PCNL), or combination of these procedures (15-17). Open or laparoscopic surgery is rarely needed to remove an encrusted DJ stent (18).

Another important issue on FUS is the medicolegal consequences. Although patients are well informed with their in situ DJ stents, any complication related to FUS will be the responsibiliy of the attending surgeon. Duty et al. reviewed closed malpractice claims in New York State and revealed that in a total of 585 claims against the urologist, 4 claims were due to retained DJ stents (19). Failure to arrange proper follow-up resulting in retained DJ stents was alleged in 27% of dismissed cases. In a similar study, Osman and Collins reviewed data on urological litigation within the UK National Health Service (NHS) between the years 1995 and 2009 (20). The largest category for dissatisfaction with care was postoperative-related claims, and within these, forgotten ureteral stents were 23 cases in a total of 168 claims.

Besides the identification of the risk factors, the development of an effective method for the prevention of FUS is quite important. In order to prevent FUS, a number of patient registry system has been used. Tang et al. tested card registry system in this manner (8). They retrospectively reviewed their card registry for a 5-year-period and

reported a 94.1% success rate in registering the patients. However, the registry of 5.9% has been missed in operating theatre due to human error. Additionally, 25% of the patients had no records of stent extraction. The card registry system was concluded to be ineffective. Similarly, Thomas et al. evaluated their ureteral stent logbook system and reported that 22.4% of the patients were unaccounted, largely as the stent removal was not documented by the surgeon (21). These written sytems seem to be ineffective since they need teamwork for double-checking and paperwork. Also, remote access to the registry is not possible.

Electronic patient registries and computer-based tracking systems were also described to prevent FUS. In 1996, McCahy and Ramsden introduced a computer database which was reviewed by administrative staff monthly to capture patients with overdue stents (22). They demonstrated a reduction in the number of overdue DJ stents from 3.6% to 1.1%. Ather et al. also reported a computer database that reduced the rate of overdue stents from 12.5% to 1.2% (23). Even though these systems were better than the card registry systems, they still required manual data entry and manual review. In 2007, Lynch at al. reported an electronic stent register which was integrated to the network and EMR system of the hospital (9). After stent insertion and entry of maximal stent life, this system sent a notice by e-mail to clinical staff if a stent became overdue for removal. They reported that 13% of the stents were not captured even after barcode implementation. Although this electronic registry system was more succesful than paper-based systems, it needed specific programs and access to the network of the center. To eliminate the uncaptured stent problem, Baumgarten at al. described a billing-based system where the entry of the ICD-9 ureteral catheterization code with CPT and HCPCS codes to the system automatically recorded the patient to the stent registry and sent an HIPAA compliant reminder letter to the patient (24). However, this system has incorrectly captured many patients with non-ureteral stents. Some other computer-based stent registries sending SMS reminders instead of e-mails have also been described (10, 25).

All the mentioned systems have some limitations. In the card-based systems, human factor is a main limitation. Manual entry and review are needed in addition to a lot of paperwork. Loss of patient records and archiving are also problems. Although electronic registries and computer--based systems have some advantages over card--based systems, they need specific programs, access to the hospital network, and extra costs. Moreover, these systems are only available to their developer-institutions which are usually high volume centers.

With the advances in cellular phone technology, medical applications running on smartphones have started to develop rapidly. In 2017, Molina et al. reported their retrospective study using the UST (11). In this study, 77% of stents were removed on time while 9% were overdue. However, remaining 14% were scheduled to be removed by the time of analysis. Only 1 out of 194 patients were lost to follow-up. After this study, Ziemba et al. reported that 3 out of 115 patients (3%) who did not return for their scheduled stent removal could be identified only through the UST application (26). In our study, using UST, we could easily identify patients who failed to return for stent removal. In addition, these patients had less overdue times compared to patients with appoinment cards. However, all patients with overdue times can not be cathegorized as FUS. The majority of patients with overdue times returned for removal in a safe period. On the other hand, 3 patients in the appoinment card group who did not return after 6 weeks of maximal waiting period can be considered as FUS candidates.

Despite the advantages of UST over previously described systems, there are some weak points. First, the UST is not integrated to the institutional EMR. Secondly, there is no other alternative for the registry of stent removal by an urologist other than the follower. Our study has some limitations; the number of patients is not high, and we had to limit the maximal waiting period to 6 weeks due to ethical reasons. Additionally, closer follow-up of the patients in group 1 and no phone calls for group 2 until the maximal waiting period was reached might bring about a bias and better outcomes for group 1.

CONCLUSIONS

We found that the patients with indwelling DJ stents who were followed by the smartphone--based UST application has significantly less overdue times and lost to follow-up cases. The UST is secure and easy to use POC application, and it allows urologists to check their patients out of the institute since it is cloud-based. Compared to basic appointment card system, the UST allows effectivelly tracking of the patients with indwelling stents and identifying them more quickly if they fail to return for stent removal.

ABBREVATIONS

HIPAA = Health Insurance Portability and Accountability Act of 1996

EMR = Electronic Medical Record

ICD-9 = International Classifications of Disease, 9th revision

CPT = Current Procedural Terminology

HCPCS = Healthcare Common Procedure Coding System

OR = Operating Room

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Ethics Commitee Approval

This study was approved by the Health Sciences University, Tepecik Training and Research Hospital Ethics Commitee (Approval number: 2018 / 3-5, 04.04.2018).

Compliance with Ethical Standards

Consent form was filled out by all study participants.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Treatment Options and Outcomes of Penile Constriction Devices

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ABSTRACT

Purpose: To study the effect of penile constriction devices used on a large series of patients who presented at our emergency facility. We explored treatment options to prevent a wide range of vascular and mechanical injuries occurring due to penile entrapment.

Materials and Methods: Between January 2001 and March 2016, 26 patients with penile entrapment were admitted to our facility and prospectively evaluated.

Results: The time that elapsed from penile constrictor application to hospital admission varied from 10 hours to 6 weeks (mean: 22.8 hours). Non-metallic devices were used by 18 patients (66.6%) while the other nine (33.4%) had used metallic objects. Acute urinary retention was present in six (23%) patients, of whom four (66.6%) underwent percutaneous surgical cystotomy and two (33.4%) underwent simple bladder catheterization. The main reason for penile constrictor placement was erectile dysfunction, accounting for 15 (55.5%) cases. Autoerotic intention, psychiatric disorders, and sexual violence were responsible in five (18.5%), five (18.5%), and two (7.4%) cases, respectively. The mean hospital stay was 18 hours (range, 6 hours to 3 weeks).

Conclusion: Penile strangulation treatment must be immediate through the extraction of the foreign body, avoiding vascular impairments that can lead to serious complications. Most patients present with low-grade injuries and use penile constrictors due to erectile dysfunction. Removal of constrictor device can be challenging. The use of specific tools for achieving penile release from constrictors is a fast, safe and effective method. Patients with urinary retention may require urinary diversion.

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INTRODUCTION

Penile strangulation is a rare emergency situation that requires proper immediate intervention to prevent a wide range of vascular and mechanical injuries. First reported in 1755 by Gaultier (1), there are many reports of penile incarceration in the international literature and most of them are single case reports.

In middle-aged and elderly men, the leading cause of penile injury by foreign bodies is the attempt to increase sexual performance or due to autoerotic intentions (2), while masturbation and sexual curiosity are the leading causes

in male adolescents. In infants and children, the foreign body is usually a string (3), thread (4) or hair tied around the penis. Psychiatric disorders can occur at any group age, leading patients to the application of penile constrictors and therefore incarceration.

A variety of objects of different nature (metallic and nonmetallic) have been used for this purpose, all with a similar feature, circularity. Entrapment of the penis by an encircling object leads to a range of vascular injuries that begins with penile swelling distal to the object due to the initial blockage of venous and lymphatic return. After a few hours of incarceration, compartmental syndrome arises that may result in tissue necrosis and gangrene, especially when associated with arterial obstruction. A variety of mechanical injuries can be inflicted upon the entrapped penis, including skin ulceration, urethral injuries, constriction of the corpus spongiosum and corpora cavernosa, urethral fistula development, and loss of distal penile sensation (5-7).

Penile entrapment is usually challenging to urologists working in the emergency room and surgeons must creatively use the best medical instruments and ordinary tools available in hospital facilities. Sometimes non-medical professionals are called and can be very helpful.

The aim of this study is to evaluate the clinical findings, treatment options, complications and outcomes of a large series of patients who presented at our emergency facility with penile entrapment.

MATERIAL AND METHODS

Between January 2001 and March 2016, 26 patients (27 cases; one patient had two episodes in a 45-day interval) with penile entrapment were admitted to our facility and prospectively evaluated.

The primary diagnostic assessment consisted of clinical history and physical examination. According to our hospital infection committee, first-generation cephalosporin was administered in all cases and a tetanus prophylaxis was given when needed.

We analyzed the time that elapsed from penile constrictor application to the hospital admission, presence of urinary retention, type of constrictor used, treatment options, early and late outcomes, and hospitalization period.

We classified the penile constrictor devices into type (metallic or non-metallic), motivation behind its use (erectile dysfunction, autoerotic, psychiatric disorders, and sexual violence), and complications according to the Bhat grading system and Silberstein modified categories (8, 9) (Table-1).

Early and late complications were defined as those that emerged within and after 30 days of penile constrictor removal, respectively.

Patients were followed at outpatient weekly visits in the first month after hospital discharge and then 4 / 4 months during the first year.

Our institutional review board approved the study. The mean follow-up was 11.8 months.

RESULTS

The patient's ages ranged from 17-68 years (mean: 45.7 years). The time that elapsed from penile constrictor application to hospital admission varied from 10 hours to 6 weeks (mean: 22.8 hours). Non-metallic devices were used by 18 patients (66.6%) while the other nine (33.4%) had used metallic objects. Acute urinary retention was present in six (23%) patients, of whom four (66.6%) underwent percutaneous surgical cystostomy and two (33.4%) underwent simple bladder catheterization. The main reason for penile constrictor placement was erectile dysfunction, accounting for 15 (55.5%) cases. Autoerotic intention, psychiatric disorders, and sexual violence were responsible in five (18.5%), five (18.5%), and two (7.4%) cases, respectively (Figure-1). The mean hospital stay was 18 hours (range, 6 hours to 3 weeks).

The most frequent constrictor type used by the patients in this study was a polyethylene terephthalate (PET) bottle, accounting for seven (26%) cases, while the less frequent objects were plastic rings, hair, and gear nuts, each of which was responsible for two (7.4%) cases. Penile entrapment release was obtained using a variety of medical instruments and tools according to constrictor type (Table-1). In three (11.1%) cases, help from the fire brigade was needed to remove the penile

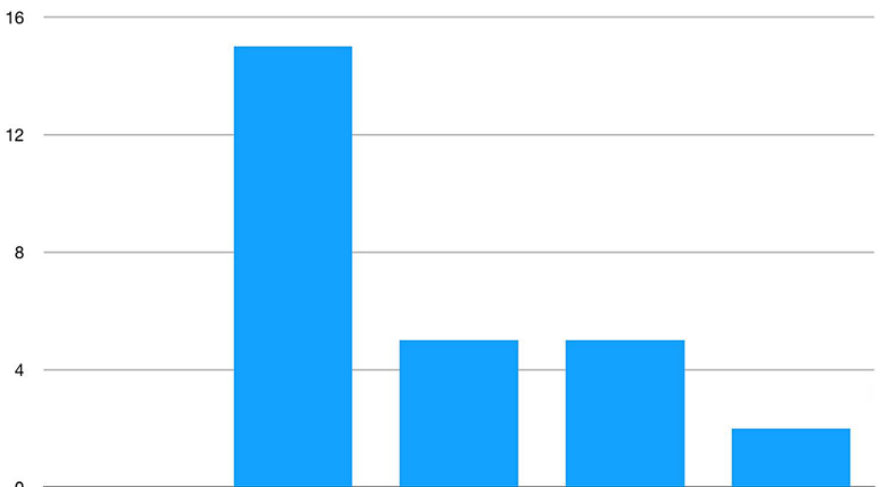
Table 1 - Treatment options for penile entrapment according to penile constrictor device and constriction injuries classification according to Bhat grading system and Sylberstein modified categories.

Penile constrictor classification (N)	Number of cases (%)	Type of constrictor	Bhat's grade system (N)	Silberstein modified categories (N)	Treatment tool option	
					Instrument options	Nunber cases
Nonmetallic (18)	07 (26%)	Pet Bottle	Grade I (4)	Low-grade (4)	Lister scissors	01
					Gigli saw	02
			Grade II (2)	Low-grade (2)	Dental drill	03
			Grade III (2)	Low-grade (1)	Orthopedics cutting pliers	04
	04 (14.8%)	Plastic tube	Grade I (2)	Low-grade (2)	Lister scissors	01
			Grade II (1)	Low-grade (1)	Gigli saw	01
					Dental drill	01
			Grade III (1)	Low-grade (1)	Orthopedics cutting pliers	01
	03 (11.1%)	PVC tube	Grade I (2)	Low-grade (2)	Gigli saw	03
			Grade II (1)	Low-grade (1)		
	02 (7.4%)	Hair	Grade I (1)	Low-grade (1)	Lister scissors	02
			Grade V (1)	High-grade (1)		
	02 (7.4%)	Plastic ring	Grade V (2)	High-grade (2)	Gigli saw	02
Metallic (9)	04 (14.8%)	Metallic ring	Grade I (3)	Low-grade (3)	Dental drill	01
					Orthopedics cutting pliers	02
				Low-grade (1)	Eletric saw	01
	03 (11.1%)	Aluminum tube	Grade I (2)	Low-grade (2)	Orthopedics cutting pliers	03
			Grade II (1)	Low-grade (1)		
	02 (7.4%)	Gear nut	Grade I (1)	Low-grade (1)	Eletric saw	02
			Grade II (1)	Low-grade (1)		

constrictor. Penile entrapment release was performed under spinal anesthesia in 03 cases (11.2%), local anesthesia in 12 cases (44.4%) and in the remaining 12 cases (44.4%) there was no need for any type of anesthesia.

Of the 27 cases evaluated, according to Bhat grading system, 15 (55.5%) consisted of grade I injuries, seven (26%) consisted of grade II injuries, and two (7.4%) consisted of grade III injuries. The remaining three (11.1%) cases involved grade V penile constrictor injuries. When stratifying patients according to Bhat's grading system for Silberstein classification, it was possible to identify 24 (88.8%) cases of low-grade lesions and three (11.2%) of high--grade lesions (Table-1).

Figure 1 - Penile constrictor application according to its etiology.



	Erectile Dysfunction	Autoerotic Intention	Psychiatric Disorders	Sexual Violence
TOTAL	15	5	5	2
PERCENTAGE (%)	55,5%	18,5%	18,5%	7,4%

The early complications included edema in 25 (92.5%) cases, necrosis and skin infection in two (7.4%) cases, and decrease / loss of penile sensation, abscess / cellulite, penile amputation, and urethra fistula in one (3.7%) case each. The late complications included decreased / lost penile sensation in one (3.7%) patient and urethral stricture in two (7.4%) cases (Table-2).

After hospital discharge, all patients were referred to our sexual dysfunction department for follow-up and evaluation.

DISCUSSION

Penile strangulation is a rare urological emergency. The presentation of each case varies, and removing the constriction devices can present great challenges. A variety of types of metallic and non-metallic constriction devices have been used, ranging from simple plastic rings to rubber bands, hair, hammerheads, soft drink bottles, and, most frequently, various metal rings (9-11). In our series, the majority of patients (66.6%) used non-

Table 2 - Early and late complications after penile constrictor release.

	No. Complication (%)	
Complication	Early	Late
Edema	25 (92.5)	0
Wound infection	2 (7.4)	0
Loss penile sensation	1 (3.7)	1 (3.7)
Cellulite	1 (3.7)	0
Penile amputation	1 (3.7)	0
Urethral fistula	1 (3.7)	0
Urethral stricture	0	2 (7.4)

-metallic constriction, while the others (33.4%) used metallic devices.

The complications of penile strangulation vary and depend on factors including type of device used, degree of constriction, and time elapsed until presentation. Several authors have attempted to grade such injuries. Bhat et al. developed a grading system for penile injuries and divided them into five categories ranging from penile edema to gangrene (8). Grade I causes only edema, while Grade II involves penile paresthesia. Grade III involves injury to the skin and urethra but no urethral fistula. Grade IV involves urethral fistula. Grade V injury involves gangrene, necrosis, or complete amputation. Further, Silberstein et al. simplified this grading system by modifying it into two broad categories (9). Low-grade injuries include penile edema, ulceration of skin, and decreased penile sensation with no evidence of a urethral fistula. High-grade injuries are defined as injuries that are likely to require surgical intervention. In our experience, the most common type of injury, according to the Bhat grading system, was grade I in 15 (55.5%) cases and only three (11.1%) cases of grade V. When stratifying patients according to Bhat's grading system for Silberstein classification, we found 24 (88.8%) cases of low-grade lesions and three (11.2%) cases of high-grade lesions (Table-1).

Regardless of the treatment option, the main objective is removal of the constricting device to restore venous and lymphatic drainage and arterial inflow, preserving the organ's anatomy and functionality. This approach must be delivered urgently since prolonged placement of constriction devices is considerably more likely to result in high-grade injuries. According to Broderick et al. in a study using color Doppler ultrasonography, penile incarceration > 30 minutes may result in penile ischemia (12). Despite this, the mean time that elapsed from penile constrictor application to hospital admission in our series was 22.8 hours.

The main reasons for this delay are patient shame and psychiatric disorders. We had two cases in which penile amputation was required, both of which involved late presentation. In the first case, the patient was 16 years old and had a psychiatric disorder. He first used hair as a penile constrictor; after 45 days, he returned to our emergency department with a new penile strangulation for 48 hours when the distal end of the penis fell off due to necrosis. The patient was taken to the operating room for penile debridement. In the other case, the patient presented to our hospital after 72 hours of using a plastic ring as a constrictor. Even after device removal, the patient developed necrosis and infection of distal third of the penile shaft (Figure-2). After conservative treatment with antibiotics and debridement, the evolution was unfavorable and the patient underwent a partial penectomy.

The type of constricting device appeared to impact the degree of penile injury, with the more severe injuries induced by non-metallic devices. Non-metallic constricting devices accounted for 2 / 2 (100%) of high-grade penile injuries in our series, while metallic constrictors did not produce any high-grade lesions (0%). The increased elastic properties of non-metallic items makes them easier to position, but during the edema phase might be more likely to exert pressure on the penis, resulting in lesions of greater degree.

There are many reports of different devices that have been used as well as techniques and suggestions for their removal (13, 14). The approach of choice depends on the type of the constricting

Figure 2 - Patient with penile incarceration produced by a plastic ring with signs of tissue impairment of the distal penile shaft.

device, degree of injury, and available equipment (9). Penile aspiration could serve as the simple first step to reduce edema and provide more space to release the device (15). Katz et al. described a new noninvasive technique, the "pseudo-pulley" method, which involves the passage of four straight Nitinol hydrophilic guide wires to remove a penile constriction device (16). If non-invasive removal is not possible, an object may be cut or sawed off. Nonelectric cutting tools should be reserved for smaller and softer objects such as hair, plastic bottle rings, and smaller metal rings (17). Unfortunately, there are some reports of iatrogenic injury caused by these devices (18). Horstmann et al. reported the successful removal of a 3.6-cm long piece of heavy metal tubing using an angle grinder (19). In cases when all other extraction techniques have failed and there exists devitalized or gangrenous tissue, penile degloving and amputation can be employed (9).

In our series, a Gigli saw (44.4%) was most commonly used to remove non-metallic penile constrictors, followed by orthopedic cutting pliers (22.2%). Gigli saws are manufactured with several interlaced micro-twisted and then braided steel strands that give them great cutting power. They are easily applied under the penile constrictor, allowing them to be removed quickly and non-invasively, constituting an excellent option for the removal of non-metallic constrictors devices (Figure-3).

Unlike non-metallic penile constrictors that can usually be removed simply by incising the constriction device, metallic constrictor removal can be a challenge. In our series, the most commonly used device for removing metallic constrictor devices was the orthopedic cutting plier (55.5%), followed by the electric saw (33.3%) and dental drill (11.2%). There are several orthopedic pliers on the market whose cutting capacity can reach up to 0.9 cm thicknesses. The orthopedic cutting plier used in our institution was able to cut metal objects up to 0.8 cm thick (Figure-4). In three cases in which the metallic object had a thickness > 1.0 cm, the removal was done using an electric saw and dental drill manipulated by the fire brigade and the dentist on duty. Specialized teams that work with electrical devices are more proficient than urologists and should perform the extrication to avoid accidents (20). The use of a protective barrier between the foreign body and the penis is recommended, especially when electric devices are employed, to avoid iatrogenic injuries (21).

Figure 3 - Patient with penile incarceration produced by plastic tube (A+B). Gigli saw used to remove the foreign body (C). Final appearance of the penile shaft after penile constrictor removal (D).

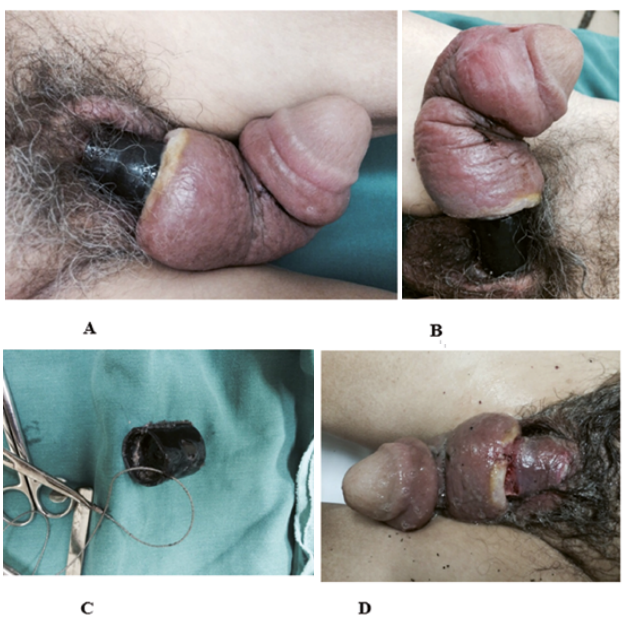
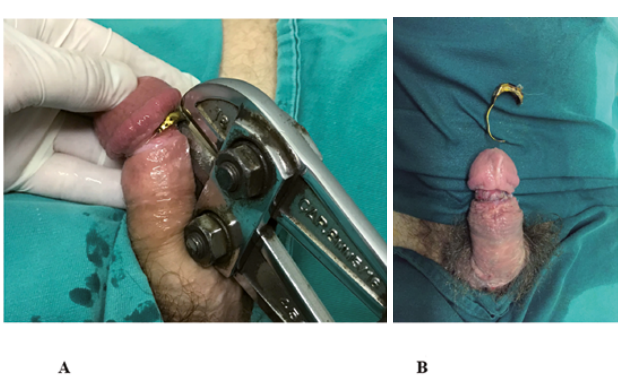


Figure 4 - Patient with penile incarceration produced by metallic ring. Metallic ring removal through orthopedic cutting plier (A). Final appearance of the penile shaft after penile constrictor removal (B).



Acute urinary retention may occur due to urethral compression or injury produced by the

foreign bodies. In our series, six patients (23%) presented with urinary retention that required bladder catheterization or supra-pubic catheter placement. A urethral evaluation may be necessary in cases of urethral fistula formation or suspected urethral stenosis. In this series, one (3.7%) patient developed a urethral fistula and two (7.4%) patients developed urethral stenosis. All patients were referred to the department of reconstructive surgery where they underwent urethroplasty through longitudinal penile skin flap. After the follow-up period, none of our patients reported lower urinary tract symptoms.

Depending on the severity of the injury caused by the constriction device, post-extraction complications can occur. Penile edema is the most common complication seen after constrictor extraction, with spontaneous resolution through re-establishment of venous and lymphatic drainage. In this series 25 (92.5%) patients developed penile edema with spontaneous resolution within 10 days. In exceptional cases, large penile edema can limit penile arterial blood flow, so color Doppler ultrasonography may aid in determining the vascular patency (21).

Lost or decreased penile sensation is an uncommon complication arising from the use of penile constrictor. It is probably related to the compression of the penile innervation exerted by the foreign body as well by the decrease of blood inflow in the affected area. In this series only 1 (3.7%) patient developed this condition whose resolution was spontaneous within 02 months, with no need of further treatments.

To our knowledge, this is the largest series published in the international literature.

CONCLUSIONS

Penile strangulation is a rare urological emergency whose treatment must be immediate through the extraction of the foreign body, avoiding vascular impairments that can lead to serious complications. Most patients present with low-grade injuries and use penile constrictors due to erectile dysfunction. There are some treatment options, but depending on the case, their removal can be challenging. The use of specific tools for achieving penile release from constrictors is a fast, safe and effective method. Patients with urinary retention may require urinary diversion.

CONFLICT OF INTEREST

None declared.

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CHALLENGING CLINICAL CASES

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Crossover transseptal vasovasostomy: alternative for very selected cases of iatrogenic injury to vas deferens

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ABSTRACT

Inguinal herniorraphy is a possible cause of iatrogenic seminal tract obstruction. Diagnosing and correcting these vasal injuries can be challenging. Successful re-anastomosis is technically challenging, with relatively low success rates. An uncommon alternative for selected cases is the crossover transseptal vasovasostomy. We herein report a case of a 36-year-old male patient with vas deferens injury after herniorraphy and a contralateral hypotrophic testis. He was successfully treated through microsurgical crossover transseptal vasovasostomy, with spontaneous pregnancy achieved, and the technique is presented in details.

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Keywords:
Azoospermia; Herniorrhaphy; Infertility; Vasovasostomy

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INTRODUCTION

Inguinal herniorraphy is a possible cause of iatrogenic seminal tract obstruction. Vas deferens injury, estimated to occur in 0.3% to 2.0% of herniorrhaphies, is not usually recognized at the time of hernia repair (1). If the patient sustains only a unilateral obstruction with a normal contralateral testicle and patent duct, the injury may remain unnoticed. However, if there is bilateral injury, a congenital absence of the contralateral vas or an abnormal contralateral testis, the patient will be rendered infertile (1-3).

Diagnosing and correcting these vasal injuries can be challenging. The obstruction is commonly associated with significant scarring at the inguinal region. Successful re-anastomosis is technically challenging, with relatively low success rates (4-7). An uncommon alternative for selected cases is crossover transseptal vasovasostomy (8-10). We herein report a case with successful application of this technique.

Case report

A 36-year-old male patient with secondary infertility was admitted to our clinic. He had a 30-year-old wife with regular menstrual cycle and without gynecologic pathology on examination. He underwent right inguinal hernia repair three years prior to this first evaluation, after their first

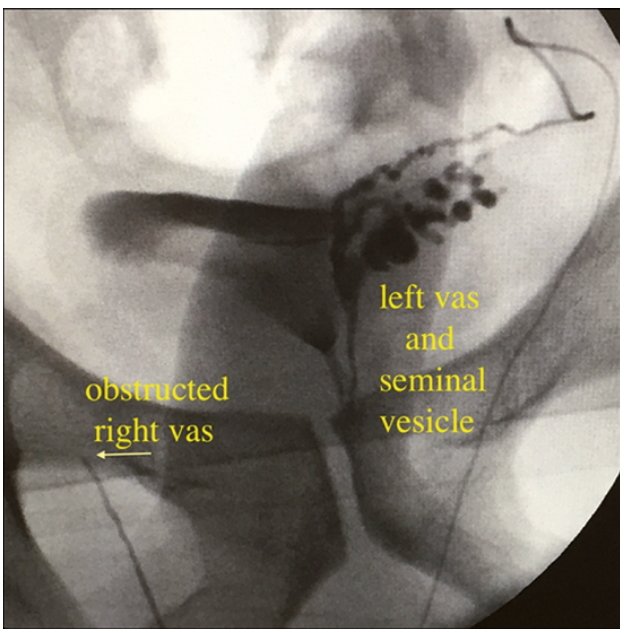
son was born. Sperm parameters were as follows: semen volume, 2.3cc; sperm count 3.0 x 10^6 / mL; motility, 0%; and Kruger morphology 0%. Follicle stimulating hormone (FSH = 3.0mUi / mL), luteinizing hormone (LH = 3.9mUI / mL) and testosterone levels (350.1ng / dL) were within the normal range.

On his physical examination, right testicular volume was normal (11.7cc) and left testis was hypotrophic and retractile (7.3cc). No varicoceles could be detected neither on physical nor on ultrasound examination. His medical history did not reveal significant factors. Even though the patient wasn't azoospermic, the severe spermatic oligoasthenoteratospermia was incompatible with the prior pregnancy history. As the couple had a prior son and the only relevant factor was the inguinal hernia repair, it was suspected that a right vas deferens obstruction had occurred, and the associated left testicular atrophy was responsible for the low semen parameters. Facing the diagnosis, they decided to undergo intracytoplasmic sperm injection (ICSI); but after five unsuccessful procedures, with two unexplained miscarriages, the couple returned to attempt a surgical treatment.

Surgical exploration of the testes was performed through a scrotal incision. After dissection of the vas deferens, a 23-gauge angiocatheter was placed into the lumen and contrast was injected to assure patency and confirm the diagnosis of obstruction (Figure-1). The catheter was placed in the segment planned to perform the anastomosis, assuring a long distal segment with the adequate (right) testicle and a long proximal segment in the side of the adequate (left) vas deferens (Figure--2A). After confirming the presence of spermatic fluid, a sufficient length of normal vas on the contralateral side was tunneled through an opening in the scrotal septum, and the anastomosis was performed. A 2-layer end-to-end microsurgical anastomosis with 9-0 suture was performed (Figures 2B and 3).

After one month of the procedure, a control sperm analysis was performed, and revealed: semen volume, 2.3cc; sperm count 17.0 x 10^6 / mL; motility, 6%; and Kruger morphology 1%. After 3 months, the couple got pregnant and the baby was born healthy after an uneventful pregnancy.

Figure 1 - Intraoperative deferentography demonstrating obstructed right vas deferens and normal left vas and seminal vesicle.



DISCUSSION

Inguinal hernia repair is one of the most common causes of iatrogenic vasal obstruction. The true incidence is unknown, but for a procedure performed over 20 million times annually worldwide, the risks become high (3, 7). The treatment of an inguinal hernia has changed considerably over the past decades. Polypropylene is the biomaterial most commonly used in hernia repair, and induces chronic inflammatory reaction, essential for optimal fixation and incorporation of the prosthesis. However, especially in the laparoscopic procedures that are mainly performed nowadays, the mesh is placed in close contact with the vas deferens, what can theoretically lead to an obstruction of these structures. Previous authors have reported several patients with postoperative obstructive azoospermia after hernia repair with polypropylene meshes (3-6, 8). This complication however can only be noted in men who undergo bilateral mesh repair for inguinal hernias and those who undergo a unilateral repair with impairment of contralateral testis. An additional factor is that fertility concerns might be present, what do

Figure 2 - A) Schematic view of iatrogenic injury to right vas deferens with hypotrophic left testis. B) Schematic view of surgical procedure for microsurgical crossover transseptal vasovasostomy.

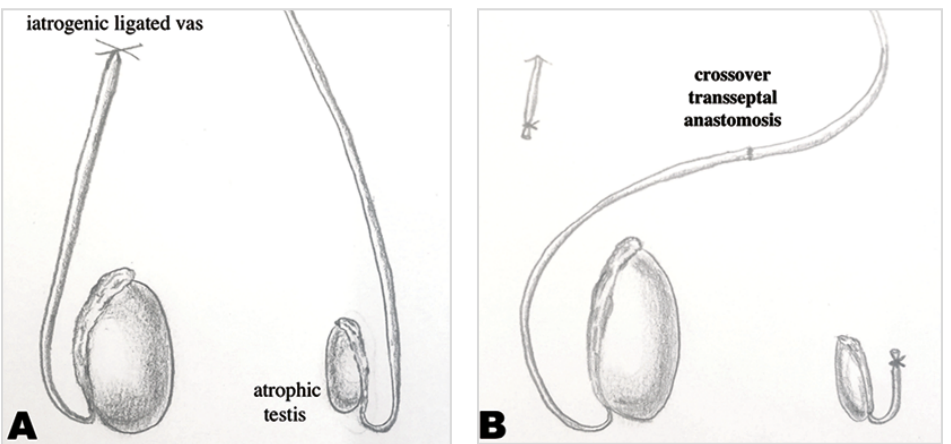
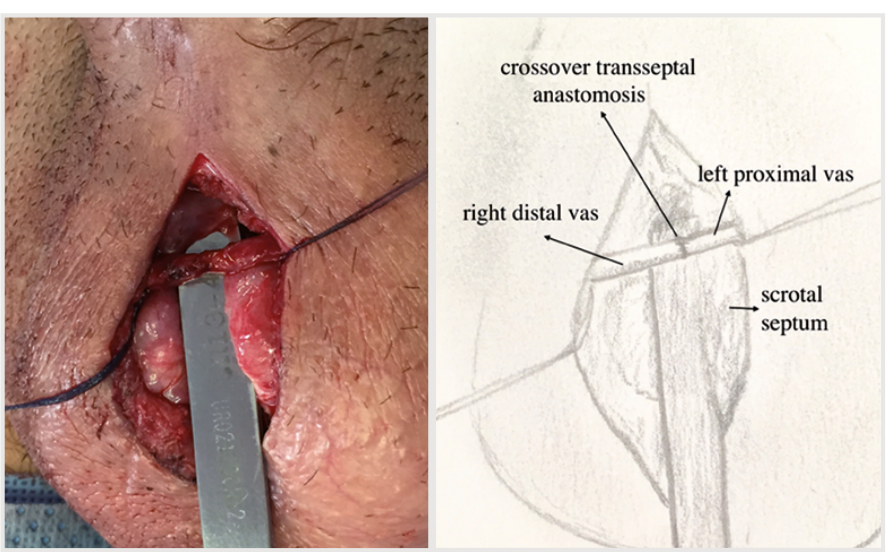


Figure 3 - Final aspect of the microsurgical crossover transseptal vasovasostomy.



not occur frequently in the elderly population that most commonly undergo such procedures. To better understand these risks, there is a prospective randomized trial currently being conducted (7).

When this unfortunate condition is suspected, there are limited diagnostic tools. If the vas is obstructed due to previous hernia repair, the epididymis may be thickened or indurated. Deferentography is conclusive although invasive, and normally performed intraoperatively. A testis biopsy can also confirm spermatogenesis on the obstructed side. Attempt to perform a vasovasostomy in the herniorraphy scarred tissue is cumbersome, with relatively low success rates (2, 4, 5). Distinctive complex approaches, including robotic anastomosis have also been described (8), and might be an alternative in bilateral cases. In the present case, there was only one adequately functioning testis, and a viable contralateral vas deferens. Even though rarely described, the crossover transseptal vasovasostomy can be a relatively straightforward alternative for these cases, as it is very similar to vasectomy reversal. Results therefore are expected to be similar to these com-

monly performed procedures. Even in a series in which crossover transseptal vasoepididymostomy was required, Sabanegh & Thomas reported a patency rate as high as an 89% (9).

Advances in assisted reproductive techniques and ICSI have brought a new treatment modality for men with obstructive azoospermia. However, it is associated to additional risks and costs. Female factors, noteworthy female age, have to be meticulously considered before choosing the best approach for a specific scenario. However, if there is a solitary functioning testis with irreparable ductal obstruction, crossover transseptal vasovasostomy can be an alternative to restore patency, and might be offered as an option to these couples interesting in achieving pregnancy.

CONFLICT OF INTEREST

None declared.

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CHALLENGING CLINICAL CASES

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Iatrogenic Ureteral Obstruction During Transvaginal Oocyte Retrieval

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ABSTRACT

Transvaginal oocyte retrieval is a crucial step in assisted reproductive technology. Various complications may arise during this procedure. Ureteral injury is a rare, but a serious complication in gynecological practice. During oocyte retrieval, ureteral injuries, detachment and obstruction can be seen, though rare. In this study, we will present ureteral obstruction that develops secondary to small hematoma, which mimics ovarian cyst torsion or ruptured ovarian cyst.

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INTRODUCTION

In vitro fertilization (IVF) and embryo transfer has been established as an integral part of assisted reproductive technology worldwide (1). IVF requires several steps in sequence, including stimulation of ovarian follicles, ultrasound--guided transvaginal oocyte retrieval, in vitro fertilization of the oocytes, and transfer of one or more embryos into the uterine cavity. Complications can occur during any of these steps and may rarely result in serious sequelae. The major complications of in vitro fertilization (IVF) include ovarian hyperstimulation syndrome (OHSS), multiple pregnancy, ectopic or heterotopic pregnancy (2). Transvaginal oocyte retrieval (TVOR) is the safest method for obtaining oocytes in in-vitro fertilization (3). It is a minimally invasive surgery; however, complications associated with surgical or clinical methods may be observed in this procedure. Vaginal bleeding, pelvic vascular injury, bowel injury, pelvic abscess, bladder and ureter injuries have been reported as complications. (4-6). In this study, we present a ureteric obstruction secondary to small hematoma forming around the right orifice on inferior surface of the bladder during transvaginal oocyte aspiration.

CASE

The patient was a 35 years old woman with history of two early miscarriages and no long-term pregnancy. The physical examination revealed hirsutism and menstrual irregularity. In the anamnesis, an intramural myoma myomectomy operation was conducted through laparotomy; disc hernia and peptic ulcer were present. The patient was married for 7 years and underwent intrauterine insemination twice. Chromosome analysis performed on peripheral blood revealed a marker chromosome: 47XX+m. In ultrasonography examination, the patient was seen to have polycystic ovary appearance, but the uterus and endometrium were observed to be normal. Our case was coherent with polycystic ovarian syndrome (PCOS). On the second day of menstruation, a hormonal analysis was performed. The results were AMH- 6.4 ng / mL; Estradiol- 52.23 pg / mL; FSH- 6.16 mIU / mL; Lh- 21.22 mIU / mL; Prolactin- 10.35 ng / mL and TSH- 0.99 µIU / mL. Semen analysis was normal. Her body weight was 64 kg, and her BMI was 25 kg / m^2. After a genetic consultation, polycystic ovary appearance, recurrent miscarriages and marker chromosome were taken into consideration, and IVF and preimplantation genetic diagnosis were planned.

IVF ICSI procedure

An antagonist protocol with 187.5 IU rFSH (Gonal F, Merck, Turkey) was initiated. On the examination performed on day 6, 0.25 mg ganirelix per day (Orgalutran MSD Turkey) was initiated. She was stimulated for a total of 11 days. Due to OHSS risk, 0.2 mg triptorelin (Gonapeptyl Ferring Turkey) was used to trigger ovulation. Estradiol level on the day of triggering was 8999. The oocyte retrieval (OPU) was performed approximately 35 hours after the triggering.

Oocyte retrieval was performed by a subspecialist experienced in reproductive endocrinology and infertility using the standard transvaginal ultrasound-guided approach. The patient was prepped and draped in the dorsolithotomy position. The aspiration of ovarian follicles was carried out using a 17-gauge oocyte aspiration needle (Cook Medical Inc., Bloomington, IN) mounted on an ultrasonic transvaginal probe (Analogic Ultrasound Canada, Richmond, BC) with a needle guide and connected to a Cook Aspiration Unit (Cook Medical Inc., Bloomington, IN). 30 oocytes were collected, and IV fluid replacement and volume enhancers (Voluven Turkey) of approximately 2000 cc were given in the first 2 hours following the OPU operation. Meanwhile, severe right inguinal pain developed, and abdomen was tense. Transvaginal ultrasonography could not be performed due to pain. Abdominal ultrasonography was performed due to suspicion of ovarian torsion or ovarian cyst rupture. The right ovary measured 95 X 93 mm and the left ovary measured 104 X 96 mm. The vascularization was normal in both ovaries and no hematoma or mass was noted. The amount of free abdominal fluid was minimal. Painkillers (Diclofenac sodium and IV Paracetamol) were administered. Complete urinalysis was normal; no hematuria was detected. Pain persisted for 4 hours after the procedure, and therefore, the patient was referred to a tertiary referral hospital. According to the information received, a narcotic analgesic (Aldolan, Liba, Turkey) was administered and the patient was discharged 24 hours later since laboratory findings were the same, and pain was reduced. 40 hours after OPU operation, severe inguinal pain developed again, and the patient was hospitalized. The reason for pain could not be diagnosed. The pain intensified, and therefore, it was decided to perform exploratory laparotomy to exclude ovarian torsion or retroperitoneal hematoma. Pelvic tomography (CT) was performed on the third day prior to the laparotomy operation. Tomography revealed a hematoma, measuring 17 x 20 mm, and ureteral dilatation secondary to the hematoma on the inferior surface of the bladder, where the right ureter entered into bladder (Figure-1). When it was understood that this hematoma was the reason for ureteral obstruction, laparotomy operation was dropped. Cystoscopy was performed under general anesthesia and hematoma and edema were noted under the mucosa around right ureteral orifice. A 6F double J stent, measuring 26 cm, was inserted into the right ureter to achieve ureteric passage (Figure-2). The pain reduced dramatically after the procedure. Patient

Figure 1 - Hematoma on the inferior surface of the bladder.

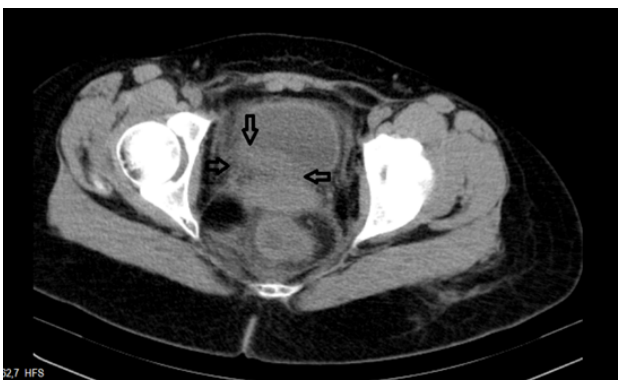
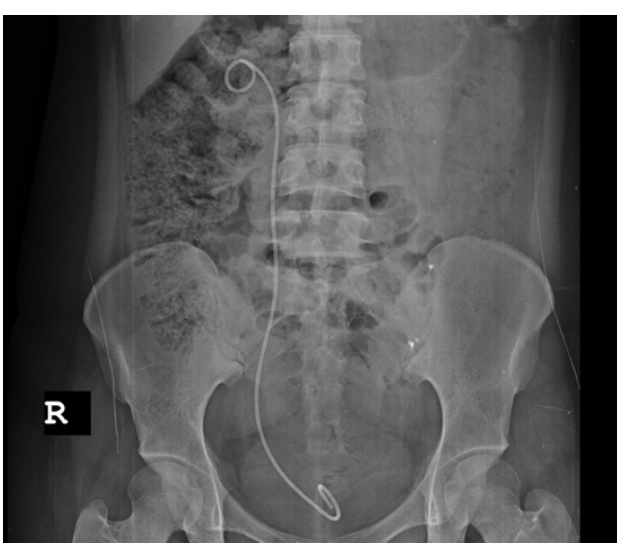


Figure 2 - Double J stent, was inserted to right ureter to achieve ureteric passage.



was discharged. The patient was examined again 21 days later, and it was noticed that hematoma had disappeared. A second cystoscopy was conducted, and catheter was removed.

Of the oocytes collected, 26 were mature. Fifteen oocytes were fertilized with intracytoplasmic sperm injection (ICSI). Four embryos reached the blastocyst stage and trophectoderm biopsy was performed. Each embryo was separately cryopreserved. Preimplantation genetic screening was performed by the Next Generation Sequencing method. Two embryos were normal; one of the four had multiple chromosomal anomalies, and the other had mosaic trisomy 15. Two normal embryos were transferred after preparing the endometrium, and two healthy babies were delivered by cesarean section after a healthy pregnancy period.

DISCUSSION

TVOR is a safe, simple and effective method. Vaginal bleeding and pelvic infection are the most common complications that occur after oocyte retrieval by ultrasound (7). Ureteral injuries are considered as serious complications of all gynecological cases; a literature review shows that ureteric complications are rare after TVOR (8). Ureteral injuries are quite rare due to its anatomical position (9). Ureteral injury risk can occur in conditions leading to anatomic irregularities, such as endometriosis, previous operations, and pelvic inflammatory diseases and due to distortion that occurs when pressure is applied by the transvaginal ultrasound probe (10).

Nausea, vomiting and pelvic pain are observed in ureteral complications that developed after oocyte retrieval, and also hematuria, abdominal distension, and vaginal discharge are detected. Transvaginal ultrasound, intravenous pyelography (IVP), or CT are recommended for diagnosis (11, 12).

The main problem in our case was the presence of polycystic ovary syndrome and hyperstimulation due to this syndrome. During TVOR, inserting a needle through the side wall of the vagina and pulling it out of the ovary were performed several times with aspiration needles in order to aspirate all follicles in the hyper-stimulated ovary. Meanwhile, hematoma developed over time on the bladder wall and around the ureteral orifice with the injury of small vessels under the bladder. We think that pelvic distortion having developed secondary to myomectomy may also have played a role in hematoma. In our case, no symptom was observed except severe right inguinal pain. Also, we focused on ovarian torsion in the acute phase, since hematuria was not present in our case, and the hematoma was not observed on the backside of the bladder, because only abdominal ultrasonography was performed. If TVUSG, CT, or IVP had

been performed in the first few hours, hematoma or distal obstruction in the ureter could have been detected.

In a similar case, a patient from India had hematoma on the uterus adjacent to right ureter. However, hematoma was evident, and the clinical picture was improved after placement of ureteral stent (6).

When a literature review is performed, it may be observed that 4 cases out of 14 had ureteral obstruction. Of two cases with ureteral stent placement, one required ureteral re-implantation, and the other required nephrectomy secondary to renal failure (11, 13-15). Percutaneous nephrostomy has also been performed in the ureteral injury for treatment (16). In our case, ureteral stent placement was performed, and the clinical picture improved over time once hematoma was reabsorbed.

CONCLUSIONS

Ureteral injury is a very rare complication. If there are no findings such as nausea, vomiting, abdominal distension, and hematuria, it is difficult to diagnose. For early diagnosis, a CT or cystoscopy should be performed on patients suffering from severe pelvic pain to exclude hematoma or ureteral obstruction. During treatment, placing a temporary stent will dramatically reduce symptoms if the ureter is intact.

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CONFLICT OF INTEREST

None declared.

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A rare case of prostato – symphyseal fistula after GreenLight photovaporization of the prostate

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DESCRIPTION OF CASE

A 73 - year - old male patient was referred to us with worsened lower urinary tract symptoms and severe pubic pain. He had a history of benign prostate hyperplasia that was treated 2 years ago by GreenLight 180W XPS photovaporization of the prostate without intraoperative or immediate postoperative complications. At physical examination, selective pubic symphysis palpation was painful, exacerbated by ambulation. Voiding cystourethrography revealed a small contained urethral leak (Figure-1). Urethrocystoscopy showed an orifice with necrotic tissue at the 2 o'clock position of the prostatic fossa (Figure-2). The diagnosis of the anterior urinary fistula was confirmed by the presence of urine through the pubic symphysis (Figure-3A-B) in fat suppressed magnetic resonance imaging (MRI), with bone marrow edema within both pubic bones (Figure-3C). Conservative

Figure 1 - Voiding cystourethrography revealed small contained urethral leaks (black arrows).

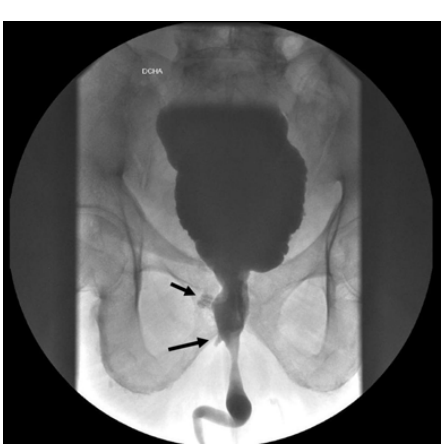
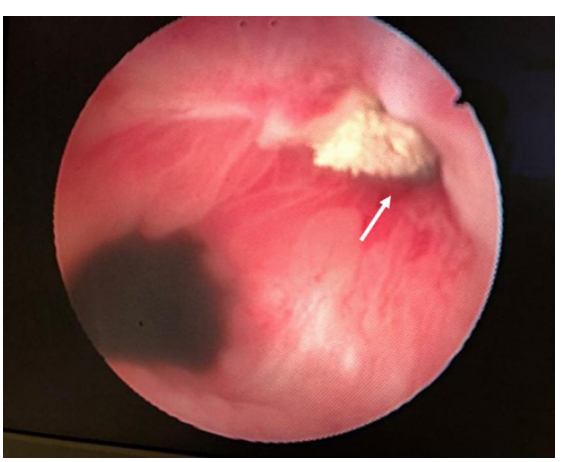


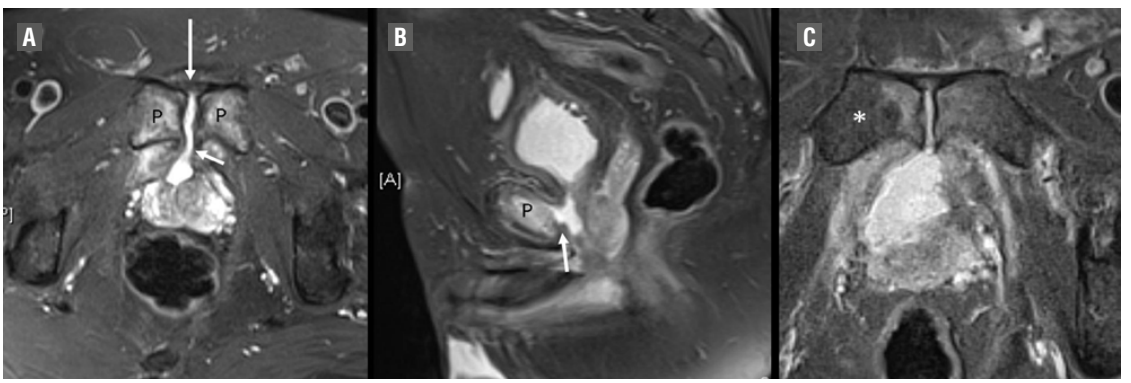
Figure 2 - Endoscopic view showing an orifice of the fistula (white arrow) located in the anterolateral region of the prostatic fossa.



treatment was planned, including transurethral catheter placement for 3 months and 6 weeks of antibiotic therapy. However, due to worsening of the symptoms, a surgical repair was scheduled and is still pending.

Urosymphyseal fistulas occur when the integrity of the urethra is compromised, allowing urine leakage into the surrounding tissues, bacterial seeding of the pubic bone with the development of pubic osteomyelitis. Prostate - symphyseal fistula (PSF) is a rare complication of transurethral resection or photovaporization of the prostate. Fistulae may develop anteriorly (pubic symphysis) or posteriorly (rectum) and may originate from the bladder, prostate, or urethra. The exact incidence of anterior fistulae is unknown. A constellation of symptoms is associated with anterior urinary fistulae including osteitis pubis,

Figure 3 - Pelvic MRI with fat suppression technique. (A) Axial T2 - weighted demonstrates the presence of urine (arrow) through the pubic symphysis (P). (B) Sagittal T2 - weighted shows anterior prostate - symphyseal fistula (arrow). (C) Axial T2 - weighted image displays edematous changes within both pubic bones, most markedly on right side (asterisk).



osteomyelitis, recurrent urinary tract infections, pelvic pain, urine leakage, and / or sepsis (1). Hence, patient quality of life is severely impacted. Patients with small prostates (< 40 mL) may be at a higher risk for capsular perforation or thinning and subsequent development of osteitis pubis, osteomyelitis and PSF. Minimal use of high - power laser application in the anterior prostate tissue is recommended, particularly in small prostates (2). Computed tomography (CT) and MRI are the two imaging modalities of choice to establish a confirmed diagnosis. CT images at excretory phase enable the assessment of the presence of urine within the joint space in the case of PSF, whereas MRI is more sensitive to show inflammatory changes within the pubis or the adjacent soft tissues (3). Management of such complex patients requires a multidisciplinary approach. Patients who fail conservative management may need to undergo open repair of the fistulous tract, including omental, peritoneal or rectus abdominis flap interposition, and open radical retropubic prostatectomy.

CONFLICT OF INTEREST

None declared.

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Primary renal angiosarcoma with extensive hemorrhage: CT and MRI findings

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ABSTRACT

Primary angiosarcomas of the kidney are very rare, but highly aggressive tumors showing poor prognosis. Patients frequently complain of flank pain, hematuria, or a palpable mass. We present a case of primary renal angiosarcoma occurring in a 61-year-old man. CT images depicted a huge exophytic mass (16 cm in diameter) in the right kidney, exhibiting extensive hemorrhage. The mass showed centripetal peripheral nodular enhancement on dynamic contrast-enhanced images. Furthermore, MR imaging revealed a tangled mesh of tumor vessels in the periphery of the mass. We suggest its inclusion in the differential diagnosis of cases of hemorrhagic renal tumors with prominent vasculature.

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INTRODUCTION

Primary renal angiosarcomas are exceedingly rare, but highly aggressive tumors showing poor prognosis (1). The etiology of primary angiosarcomas of the kidney has not yet been elucidated (2, 3). These tumors are predominantly found in older men (60-70 years of age) (2, 3). Due to the low incidence of this tumor, angiosarcoma is not usually considered in the diagnosis of renal tumors associated with retroperitoneal hemorrhage (4). In this report, we describe a case of primary renal angiosarcoma showing extensive hemorrhage with an emphasis on imaging features using dynamic CT and MRI.

CASE REPORT

A 61-year-old man was admitted to our hospital with a hematoma in the right kidney. This diagnosis had been made 20 days prior to his admission. His clinical symptoms included pallor and anemia, but physical examination revealed no rigidity or distension of the abdomen; however, he

complained of discomfort on palpation in the right flank area. The initial routine laboratory tests showed the hemoglobin level 10 g / dL (normal range: 12-18) and platelet count was 85 x 103 / mm^3 (normal, 130-450). The serum levels of blood urea nitrogen and creatinine, and urinalysis were within normal limits.

CT images (Figure-1) depicted a huge exophytic mass, measuring 16 cm in diameter, in the right kidney. The mass also exhibited extensive hemorrhage. The mass showed peripheral nodular enhancement, as shown on cortico-medullary--phase CT, accompanied by delayed centripetal filling on nephrographic and excretory-phase CT images. Meanwhile, MRI (Figure-2) demonstrated a tangled mesh of tumor vessels with signal voids in the periphery of the mass on coronal T2--weighted images, corresponding to the areas with strong enhancement on contrast-enhanced coronal MR images. There were no additional mass lesions observed in other solid organs in the abdomen. Based on these imaging findings, the differential diagnoses included hemangioma, angiosarcoma, and angiomyolipoma.

Using a transperitoneal approach, the patient underwent a radical right nephrectomy. The macroscopic appearance showed a huge mass in the right kidney that extended up to the perirenal space. The mass showed extensive hemorrhage and proliferation of the tumor vessels. The microscopic features revealed complex anastomosing channels with obvious vasoformation and endothelial papillae (Figure-3). Immunohistochemical stains tested positive for ERG, CD 34, CD 31, and Ki-67. To make a differential diagnosis, we considered the pathologies of various vascular tumors, including angiosarcomas, hemangiomas, and hemangioendotheliomas. A final diagnosis of a pri-

Figure 1 - Axial CT images of pre-contrast (A), contrast-enhanced corticomedullary (B), nephrographic (C) and excretory (D) phases depict a huge mass (arrows) with extensive hemorrhage (H) in the right kidney, which shows progressive peripheral nodular enhancement with a delayed fill-in. Note the presence of residual renal parenchyma (*).

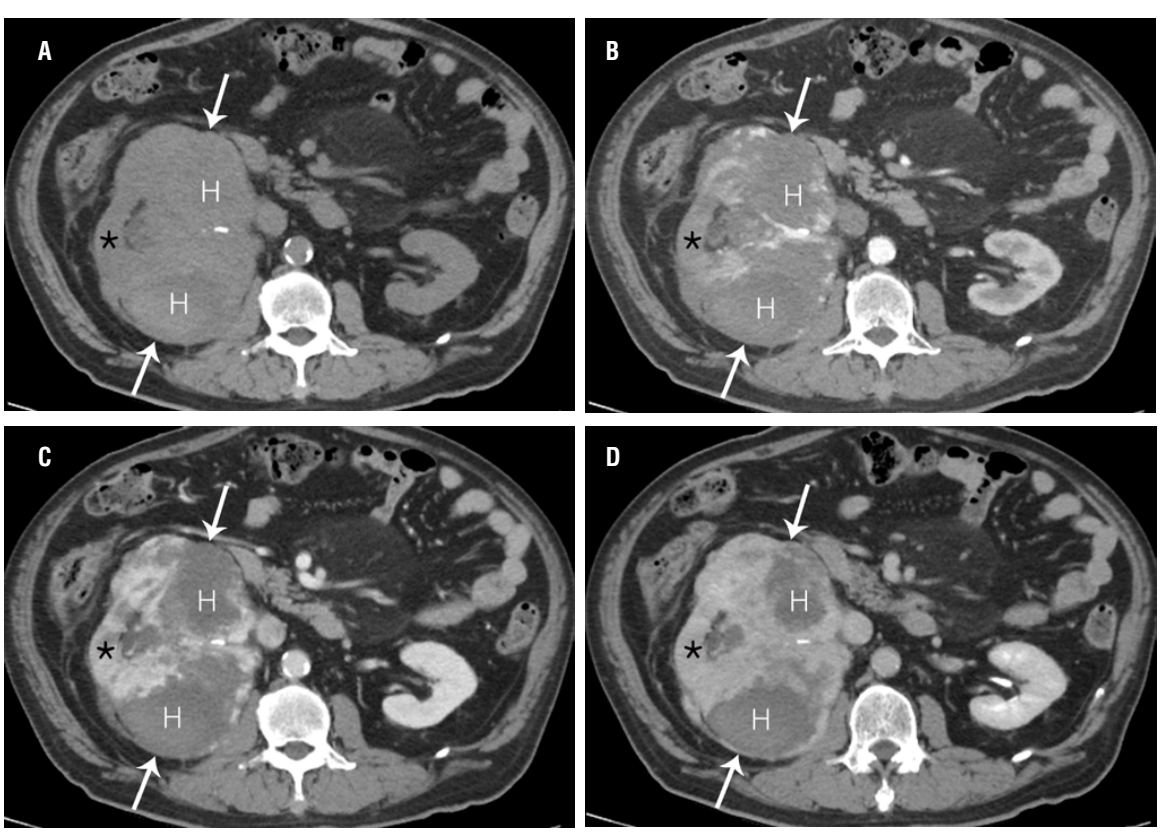


Figure 2 - Coronal T2-weighted (A) and fat-suppressed contrast-enhanced T1-weighted (B) MR images demonstrating a tangled mesh of signal-void tumor vessels (arrows in A) in the periphery of the mass, corresponding to the areas with strong enhancement (arrows in B).

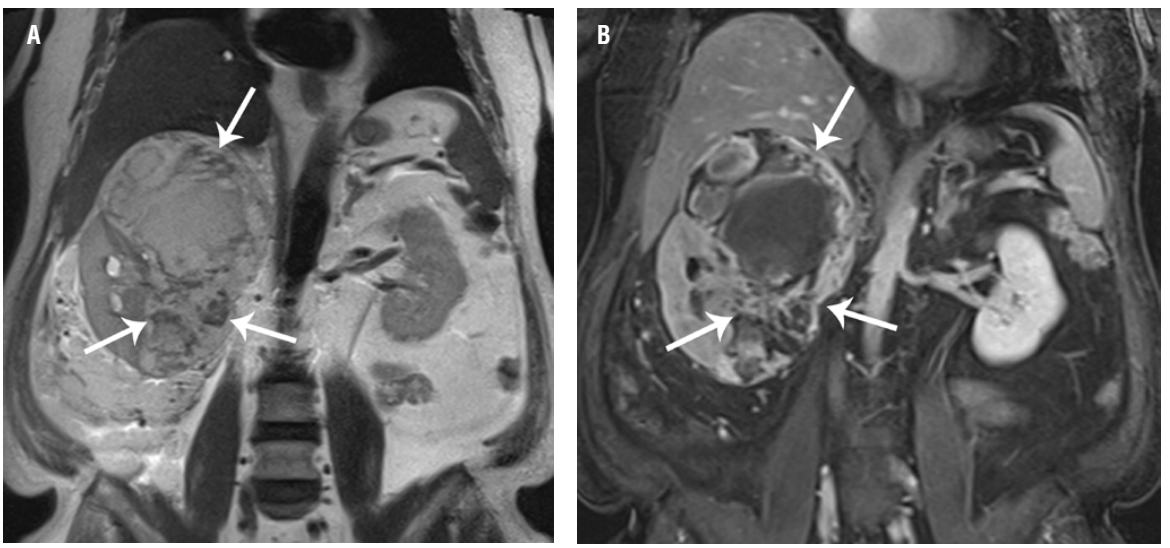
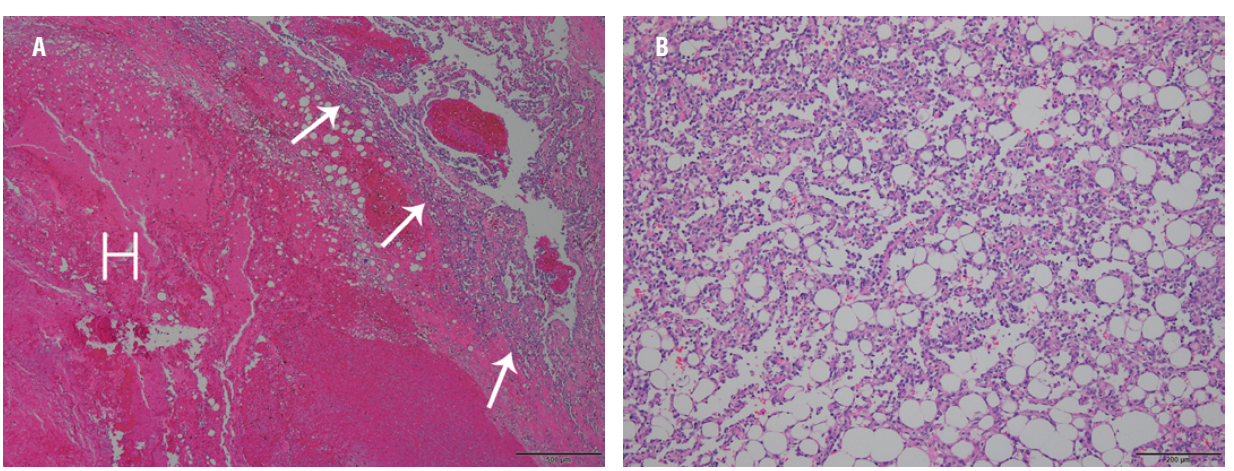


Figure 3 - Histological sections reveal hematoma (H) and anastomosing channels with obvious vasoformation and dissecting growth pattern (arrows) (A: H & E stain, x 40) and complex anastomosing channels with endothelial papillae (B: H & E stain, x 100).



mary renal angiosarcoma was made based on the aforementioned histological features.

DISCUSSION

Angiosarcoma is an aggressive malignant neoplasm originating from endothelial cells of the blood and lymphatic vessels (5, 6). Among the various malignant tumors that can occur in the kidney, primary angiosarcomas are extremely rare, with only about 64 cases reported to date in the literature (3). Although the presence of several risk factors, such as thorotrast, arsenic, polyvinyl chloride, radiotherapy, and chronic lymphedema, have been reported in angiosarcomas arising at other sites in the body, there is no evidence of a direct relationship between these predisposing factors and primary angiosarcomas of the kidney (2-4). The tumors are

usually large, measuring from 3.7 to 30 cm in diameter, and are detected in advanced stages of the disease (3).

Patients frequently present with flank pain and a palpable mass (2-4). As the tumor has a tendency to bleed, patients may also complain of massive hematuria and a retroperitoneal hematoma following spontaneous rupture of the mass (5).

With respect to imaging findings, the tumors have been described as a hypodense mass, with variable peripheral enhancement, or a large necrotic mass (1-5). However, there are very few useful imaging features, suggestive of primary renal angiosarcomas. A previous study described a striated pattern on T2-weighted MRI, as a specific finding suggestive of a primary renal angiosarcoma (7). However, in that case, the mass showed no detectable enhancement (7). In contrast, in this case, we observed early peripheral nodular enhancement accompanied by progressive fill-in on dynamic contrast-enhanced images. These imaging features may also be seen in cases of renal hemangiomas (3, 8). However, as compared to angiosarcomas, renal hemangiomas are relatively small (3). Furthermore, as seen in this case, a tangled mesh of signal-void vascular structures in the periphery of the huge mass on a T2-weighted image could be a useful MRI finding indicative of a primary renal angiosarcoma.

Due to the rarity of this tumor, there are no standard treatment guidelines for primary renal angiosarcomas (1-3, 5). However, most of the reported cases involved patients who underwent radical nephrectomies (2, 3). Radiation therapy and chemotherapy may be subsequently used in localized and metastatic disease, respectively (1, 3). The prognosis is very poor, with more than 70 percent of the reported cases dying within a mean interval of 7.3 months (3).

To summarize, we present a case of primary renal angiosarcoma with extensive hemorrhage and suggest its inclusion in the differential diagnosis of cases of hemorrhagic renal tumors with prominent vasculature.

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CONFLICT OF INTEREST

None declared.

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VIDEO SECTION

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Anterograde irrigation – assisted ureteroscopic lithotripsy in patients with percutaneous nephrostomy

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ABSTRACT

In complicated urinary tract infection with ureteral calculi, urinary diversion is inevitable. So, stenting or percutaneous drainage can be an option. In hemodynamically unstable patients, percutaneous drainage is superior to ureteral stenting (1). Once acute infection is controlled, definite treatment of the stone is necessary. According to a guideline, semirigid ureteroscopy is recommended for lower and mid - ureter stone and flexible ureteroscopy for upper ureter stone (2). Semi - rigid ureteroscopy can migrate stone to kidney, especially in upper ureter stone, lowering stone free rate (3). Not only flexible ureteroscopy creates additional costs but also is barely available in developing countries (4, 5). So, the authors would like to introduce anterograde irrigation - assisted ureteroscopic lithotripsy in patients with percutaneous nephrostomy.

Retrograde irrigation was connected and flowed minimally enough to secure visual field. Once stone is noted, another saline irrigation, which is placed above 40 cm over the patient is connected to nephrostomy. Retrograde irrigation is disconnected from ureteroscope and the previous connected channel on ureteroscope is opened. Actual pressure detected by barometer from the opened channel of ureteroscope is usually about 30 cmH_2O while anterograde irrigation is administered in maximal flow, which means fully opened anterograde irrigation is not hazardous to kidney. There was no complication in 17 patients submitted to this method.

Video shows advantages of our practice: clear visual field; reduced risk of stone migration into kidney; induced spontaneous passage of fragments without using instrumentation; and decreased operation time. In short, most of surgeons, even unexperienced, can perform an excellent procedure with less time consuming using our method.

CONFLICT OF INTEREST

None declared.

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VIDEO SECTION

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Removal of intramural trapped intrauterine device by cystoscopic incision of bladder wall

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ABSTRACT

A healthy 37 - year - old woman referred to our clinic with one - year history of recurrent urinary tract infection, dysuria and frequency. Her past medical history informed us that an IUD (Copper TCu380A) had been inserted 11 years ago. Eleven months after the IUD insertion she had become pregnant, unexpectedly. At that time, she had undergone gynecological examination and abdominal ultrasound study. However, the IUD had not been found, and the gynecologist had made the diagnosis of spontaneous fall out of the IUD. She had experienced normal pregnancy and caesarian section with no complications.

On physical examination, pelvic examination was normal and no other abnormalities were noted. Urinalysis revealed microhematuria and pyuria. Urine culture was positive for Escherichia coli. Ultrasound study revealed a calculus of about 10 mm in the bladder with a hyperdense lesion. A plain abdominal radiograph was requested which showed a metallic foreign body in the pelvis. We failed to remove the IUD by cystoscopic forceps because it had strongly invaded into the uterine and bladder wall. Despite previous papers suggesting open or laparoscopic surgeries in this situation (1, 2), we performed a modified cystoscopic extraction technique. We made a superficial cut in the bladder mucosa and muscle with J - hook monopolar electrocautery and extracted it completely with gentle traction.

This technique can decrease the indication of open or laparoscopic surgery for extraction of intravesical IUDs. In the other side of the coin, this technique may increase the risk of uterovesical fistula. Therefore, the depth of incision is important and the surgeon should cut the bladder wall superficially with caution. Although present study is a case report which is normally classified as with low level of evidence, it seems that our modified cystoscopic extraction technique is a safe and useful method for extraction of partially intravesical IUDs.

CONFLICT OF INTEREST

None declared.

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VIDEO SECTION

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Laparoscopic approach for intravesical surgery using pneumovesicum in the management of anterior colporrhaphy mesh erosion and stones around the bladder neck

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ABSTRACT

Introduction and objective: Perforation of the bladder or urethra and erosion of the mesh after cystocele repair surgery are not uncommon and have potentially serious complications. Traditionally, surgical management of such complications has involved excision of the mesh using either a transurethral approach or open surgery. In this video, we present our experience of laparoscopic transvesical surgery for exposed mesh and stone.
Materials and methods: Patient was placed in the lithotomy position under general anesthesia and a 30° operating cystoscope was inserted under direct vision. After filling the bladder with 300 mL normal saline, a 5 - mm VersaStep™ bladeless trocar was placed 2 cm above the pubic symphysis. Two more 5 mm trocars were placed bilaterally at 3 cm intervals from the initial trocar site. The pneumovesicum state was maintained at 8 - 12 mmHg and a 5 mm telescope was introduced. Using a curved dissector and curved Mayo scissors, the exposed mesh was mobilized and removed. Interrupted 4 - 0 Vicryl sutures were used to close the defect. To localize the ureteral orifice, intravenous Indigo Carmine was used. The bladder stones were removed through the urethra using a stone basket, guided using a ureteral stent pusher.
Results: Total operation time was 55 min and the Foley catheter was removed at post - operative day 5 after postoperative cystography.
Conclusions: Excellent visualization of mesh exposure and ureteral orifice was possible under laparoscopic transvesical surgery, and reconstruction including the mucosa and muscle layer was able to be achieved. This method is useful and feasible, with minimal invasiveness and an early post - operative recovery.

CONFLICT OF INTEREST

None declared.

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VIDEO SECTION

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Robotic surgery in the management of complex pelvic endometriosis

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ABSTRACT

Introduction: Endometriosis consists in the proliferation of endometrial tissue outside of the uterine cavity, predominantly in the ovaries but also in the urinary bladder or bowel. About 10% of fertile women are affected and the main symptoms are pain, menstrual disorders and infertility. Surgery is the treatment option for those symptomatic patients in which medical treatment had no success.
Material and Methods: We report on a case of a 43 - years - old patient without urologic personal history submitted to our office because of a grade - III right - hydronephrosis. The patient, with an endometriosis diagnosis since years, presents chronic pelvic pain with the daily necessity of strong opioids intake. CT scan revealed several endometriosis implants in the uterine wall and rectum that caused right ureteral entrapment. Renography revealed a 24% function in the right kidney. After right nephrostomy a multidisciplinary committee decided surgical intervention. With robotic approach, we performed an hysterectomy with right salpingo - oophorectomy; release, resection and right ureteral reimplantation; anterior resection of the rectum and protective ileostomy. Vaginal extraction of the specimen. In this video we show the key steps of the procedure.
Results: Total operative time: 330 minutes. Total bleeding: 250 cc. Nephrostomy removal: 4 th day. Urethral catheter removal: 5 th day. Patient was discharged in the 7 th day. Ureteral JJ - stent removal: 30 th day. CT urography reveals a permeable ureteral tract with no urine leakage. Renography shows a progressive improvement of the kidney function.
Conclusions: Robotic surgery allows a correct handling of endometriosis, mainly in complex cases. It is a safe and reproducible technique with correct outcomes in selected patients. A multidisciplinary team is required.

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LETTER TO THE EDITOR

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Re: The effect of urethroplasty surgery on erectile and orgasmic functions: a prospective study

Michael S. Floyd Jr. [1], Ahmad M. Omar [1] , Andrew D. Baird [2] , Paul C. B. Anderson [3]

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To the editor,

We read with interest the recent paper by Urkmez et al examining the effects of urethroplasty on erectile and orgasmic function (1).

The authors report a prospective study involving 60 males who underwent buccal graft substitution, penile skin flap or anastomotic urethroplasty by a single surgeon and report the outcomes on both erectile and orgasmic function using the international index of erectile function (IIEF) score.

The authors conclude by stating that urethroplasty does not affect erectile, sexual or orgasmic function irrespective of surgery type, stricture location or length but acknowledge the limitations of the study including the lack of validated questionnaires.

This study does highlight one of the challenges for urethral surgeons: measuring sexual outcomes following urethroplasty. As endoscopic management of recurrent stricture disease moves towards formal urethroplasty with better long term success rates, assessing outcomes remains paramount from a patient and surgical perspective. To date, there have been limited attempts at developing specific patient reported outcomes (PROMS) for anterior urethral reconstruction (2). The first study performed to evaluate urethroplasty outcomes with a validated PROM did not assess sexual or erectile function (3). There remains a paucity of validated questionnaires available to the urethral surgeon to assess sexual function post urethroplasty. The IIEF and its short form are widely used to assess all aspects of sexual function but are not specific for urethral stricture disease and the short form does not evaluate ejaculation (4). Coursey et al evaluated sexual function after urethroplasty in 200 patients with a validated PROM and found a 30% rate of erectile dissatisfaction based on type of urethroplasty with higher rates noted in the penile flap cohort, but concluded that the rate was similar to those who underwent circumcision (5). The Brief Male Sexual Function inventory (BMSFI) was developed as an assessment tool for male sexual health but is not specific for urethral stricture disease (6). The Men's Health Sexual Questionnaire (MHSQ) is a validated questionnaire (7) and has been employed to assess ejaculatory function following urethroplasty (8) but again is not urethral stricture specific. Patel et al have specifically employed the MHSQ ejaculatory domain to assess sexual function following buccal graft for staged penile urethroplasty and reported minimal differences in erectile and ejaculatory function but reported definite changes in penile curvature, length and sensitivity (9). Barbagli et al. have developed a non validated PROM to assess the effect of bulbar

urethroplasty on sexual function and reported no erectile dysfunction post operatively but 23% of patients studied reported ejaculatory dysfunction (10).

Historically, a successful outcome following urethroplasty was based on the need for secondary intervention to improve outflow symptoms but outcomes should be all inclusive and evaluate psychological, voiding and sexual outcomes as well as quality of life with a specific, validated questionnaire.

Breyer et al have published preliminary data on the development of a patient specific outcome measure, the 32 item Urethral Stricture Symptoms and Impact Measure (USSIM), which will further address both voiding and sexual symptoms following urethroplasty (1, 11).

Undoubtedly, as the assessment (12) of urethral stricture disease becomes more elaborate measuring all outcomes following urethroplasty will become routine practice for those Urologists offering urethral reconstruction. The authors are to be commended on highlighting the lack of validated questionnaires currently available to those working in the field of urethroplasty.

Yours Sincerely,

Authors

CONFLICT OF INTEREST

None declared.

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LETTER TO THE EDITOR

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REPLY TO THE AUTHORS: Re: The effect of urethroplasty surgery on erectile and orgasmic functions: a prospective study

Ahmet Urkmez [1], Ozgur H. Yuksel [2], Emrah Ozsoy [1], Ramazan Topaktas [1], Aytac Sahin [2], Orhan Koca [1], Metin I. Ozturk [1]

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To the editor,

We would like to thank the author of the letter to the editor for her or his correct point that the lack of validated questionnaires specific in the field of urethral stricture and urethroplasty (1). Today, many questionnaires available to put towards the diagnosis of erectile dysfunction and evaluate the success of treatment. International Index of Erectile Function (IIEF), was first used in the clinical study of sildenafil and is now the most commonly used assessment questionnaire in the evaluation of erectile dysfunction with subsequent validations (2). However, the IIEF evaluation provides minimal information about the ejaculatory and orgasmic function of patients (3). Besides, validation studies on questionnaires for assessing erectile and ejaculatory functions are ongoing, even by country and language (4-6).

Sangkum et al. have reported that most patients with urethral stricture complained of sexual dysfunction, especially about reduced ejaculatory fluid (85%) and after urethroplasty, no one reported a worsening erection; and many of them reported that there was a significant improvement in erection, ejaculation, relationship with their partner, sexual activity and desire (7). Also, Erickson et al., have found that urethral reconstructive surgery affects ejaculatory functions positively while not significantly affecting erectile function or sexual dysfunction (8). Since we did not have a validated questionnaire in patients with urethral stricture, we used the IIEF questionnaire, which is the most widely used validated test in the world. Recently, case- based or diseased- based questionnaires have been increasingly used. Accordingly, there are studies related to special questionnaires for patients with urethral stricture (9, 10). But these are not validated. As stated by the author of the letter to the editor, studies in this field should continue to better investigate the effect of urethral stricture and urethroplasty surgery on orgasmic and ejaculatory functions.

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The **Results** should be presented using Tables and Figures whenever possible. Excessive Tables and Figures must be avoided. The tables should not be repeated on the text.

The **Discussion** must comment only the results of the study, considering the recent literature.

Conclusions must be strictly based on the study findings.

References should contain no more than 30 citations, including the most important articles on the subject. Articles not related to the subject must be excluded.

The Abstract must contain up to 250 words and must conform to the following style: Purpose, Materials and Methods, Results and Conclusions. Each section of the manuscript must be synthesized in short sentences, focusing on the most important aspects of the manuscript. **The authors must remember that the public firstly read only the Abstract, reading the article only when they find it interesting.**

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